

B4

## (12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau(43) International Publication Date  
9 October 2003 (09.10.2003)

PCT

(10) International Publication Number  
WO 03/082214 A2

(51) International Patent Classification<sup>7</sup>: A61K [US/US]; 3353 Lebon Drive, #302, San Diego, CA 92122 (US). SCHILLING, Christophe, H. [US/US]; 12541-G El Camino Real, San Diego, CA 92130 (US).

(21) International Application Number: PCT/US03/09751

(22) International Filing Date: 27 March 2003 (27.03.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data: 60/368,588 29 March 2002 (29.03.2002) US

(71) Applicant (for all designated States except US): GENOMATICA, INC. [US/US]; 5405 Morehouse Drive, Suite 210, San Diego, CA 92121 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): PALSSON, Bernhard, O. [US/US]; 730 Fern Glen, La Jolla, CA 92037 (US). FAMILI, Imandokht [US/US]; 10185 Camino Ruiz #132, San Diego, CA 92126 (US). COVERT, Markus, W.

(74) Agents: GAY, David, A. et al.; McDermott, Will & Emery, 4370 La Jolla Village Drive, 7th Floor, San Diego, CA 92122 (US).

(81) Designated States (national): AE, AG, AL, AM, AT (utility model), AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ (utility model), CZ, DE (utility model), DE, DK (utility model), DK, DM, DZ, EC, EE (utility model), EE, ES, FI (utility model), FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK (utility model), SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

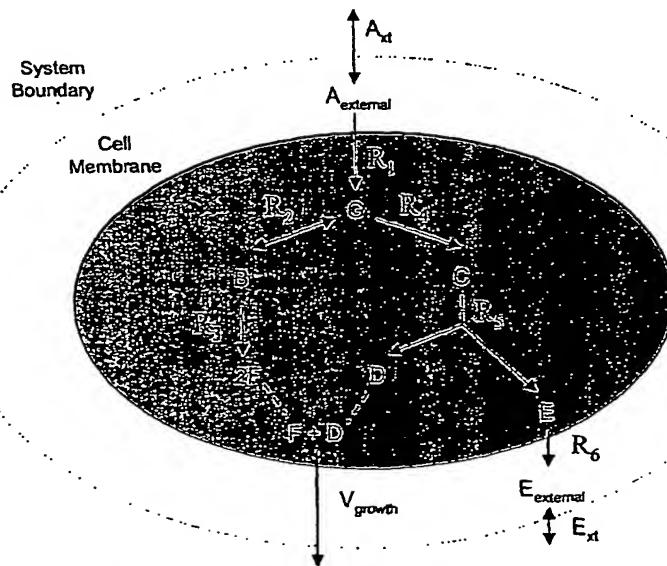
(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,

[Continued on next page]

## (54) Title: HUMAN METABOLIC MODELS AND METHODS



WO 03/082214 A2



(57) Abstract: The invention provides *in silico* models for determining the physiological function of human cells, including human skeletal muscle cells. The models include a data structure relating a plurality of *Homo sapiens* reactions, a constraint set for the plurality of *Homo sapiens* reactions, and commands for determining a distribution of flux through the reactions that is predictive of a *Homo sapiens* physiological function. A model of the invention can further include a gene database containing information characterizing the associated gene or genes. A regulated *Homo sapiens* reaction can be represented in a model of the invention by including a variable constraint for the regulated reaction. The invention further provides methods for making an *in silico* *Homo sapiens* physiological function using a model of the invention.

BEST AVAILABLE COPY



SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

**Published:**

- *without international search report and to be republished upon receipt of that report*

## HUMAN METABOLIC MODELS AND METHODS

BACKGROUND OF THE INVENTION

This invention relates generally to analysis of the activity of chemical reaction networks and, more 5 specifically, to computational methods for simulating and predicting the activity of *Homo sapiens* reaction networks.

Therapeutic agents, including drugs and gene-based agents, are being rapidly developed by the 10 pharmaceutical industry with the goal of preventing or treating human disease. Dietary supplements, including herbal products, vitamins and amino acids, are also being developed and marketed by the nutraceutical industry. Because of the complexity of the biochemical 15 reaction networks in and between human cells, even relatively minor perturbations caused by a therapeutic agent or a dietary component in the abundance or activity of a particular target, such as a metabolite, gene or protein, can affect hundreds of biochemical 20 reactions. These perturbations can lead to desirable therapeutic effects, such as cell stasis or cell death in the case of cancer cells or other pathologically hyperproliferative cells. However, these perturbations can also lead to undesirable side effects, such as 25 production of toxic byproducts, if the systemic effects of the perturbations are not taken into account.

Current approaches to drug and nutraceutical development do not take into account the effect of a perturbation in a molecular target on systemic cellular 30 behavior. In order to design effective methods of

repairing, engineering or disabling cellular activities, it is essential to understand human cellular behavior from an integrated perspective.

Cellular metabolism, which is an example of a process involving a highly integrated network of biochemical reactions, is fundamental to all normal cellular or physiological processes, including homeostasis, proliferation, differentiation, programmed cell death (apoptosis) and motility. Alterations in cellular metabolism characterize a vast number of human diseases. For example, tissue injury is often characterized by increased catabolism of glucose, fatty acids and amino acids, which, if persistent, can lead to organ dysfunction. Conditions of low oxygen supply (hypoxia) and nutrient supply, such as occur in solid tumors, result in a myriad of adaptive metabolic changes including activation of glycolysis and neovascularization. Metabolic dysfunctions also contribute to neurodegenerative diseases, cardiovascular disease, neuromuscular diseases, obesity and diabetes. Currently, despite the importance of cellular metabolism to normal and pathological processes, a detailed systemic understanding of cellular metabolism in human cells is currently lacking.

Thus, there exists a need for models that describe *Homo sapiens* reaction networks, including core metabolic reaction networks and metabolic reaction networks in specialized cell types, which can be used to simulate different aspects of human cellular behavior under physiological, pathological and therapeutic conditions. The present invention satisfies this need, and provides related advantages as well.

SUMMARY OF THE INVENTION

The invention provides a computer readable medium or media, including: (a) a data structure relating a plurality of *Homo sapiens* reactants to a plurality of *Homo sapiens* reactions, wherein each of the *Homo sapiens* reactions includes a reactant identified as a substrate of the reaction, a reactant identified as a product of the reaction and a stoichiometric coefficient relating the substrate and the product, (b) a constraint set for the plurality of *Homo sapiens* reactions, and (c) commands for determining at least one flux distribution that minimizes or maximizes an objective function when the constraint set is applied to the data representation, wherein the at least one flux distribution is predictive of a *Homo sapiens* physiological function. In one embodiment, at least one of the *Homo sapiens* reactions in the data structure is annotated to indicate an associated gene and the computer readable medium or media further includes a gene database including information characterizing the associated gene. In another embodiment, at least one of the *Homo sapiens* reactions is a regulated reaction and the computer readable medium or media further includes a constraint set for the plurality of *Homo sapiens* reactions, wherein the constraint set includes a variable constraint for the regulated reaction.

The invention provides a method for predicting a *Homo sapiens* physiological function, including: (a) providing a data structure relating a plurality of *Homo sapiens* reactants to a plurality of *Homo sapiens* reactions, wherein each of the *Homo*

*sapiens* reactions includes a reactant identified as a substrate of the reaction, a reactant identified as a product of the reaction and a stoichiometric coefficient relating the substrate and the product; (b) 5 providing a constraint set for the plurality of *Homo sapiens* reactions; (c) providing an objective function, and (d) determining at least one flux distribution that minimizes or maximizes the objective function when the constraint set is applied to the data 10 structure, thereby predicting a *Homo sapiens* physiological function. In one embodiment, at least one of the *Homo sapiens* reactions in the data structure is annotated to indicate an associated gene and the method predicts a *Homo sapiens* physiological function 15 related to the gene.

The invention provides a method for predicting a *Homo sapiens* physiological function, including: (a) providing a data structure relating a plurality of *Homo sapiens* reactants to a plurality of 20 *Homo sapiens* reactions, wherein each of the *Homo sapiens* reactions includes a reactant identified as a substrate of the reaction, a reactant identified as a product of the reaction and a stoichiometric coefficient relating the substrate and the product, 25 wherein at least one of the *Homo sapiens* reactions is a regulated reaction; (b) providing a constraint set for the plurality of *Homo sapiens* reactions, wherein the constraint set includes a variable constraint for the regulated reaction; (c) providing a condition-dependent 30 value to the variable constraint; (d) providing an objective function, and (e) determining at least one flux distribution that minimizes or maximizes the objective function when the constraint set is applied

to the data structure, thereby predicting a *Homo sapiens* physiological function.

Also provided by the invention is a method for making a data structure relating a plurality of 5 *Homo sapiens* reactants to a plurality of *Homo sapiens* reactions in a computer readable medium or media, including: (a) identifying a plurality of *Homo sapiens* reactions and a plurality of *Homo sapiens* reactants that are substrates and products of the *Homo sapiens* 10 reactions; (b) relating the plurality of *Homo sapiens* reactants to the plurality of *Homo sapiens* reactions in a data structure, wherein each of the *Homo sapiens* reactions includes a reactant identified as a substrate of the reaction, a reactant identified as a product of 15 the reaction and a stoichiometric coefficient relating the substrate and the product; (c) determining a constraint set for the plurality of *Homo sapiens* reactions; (d) providing an objective function; (e) determining at least one flux distribution that 20 minimizes or maximizes the objective function when the constraint set is applied to the data structure, and (f) if the at least one flux distribution is not predictive of a *Homo sapiens* physiological function, then adding a reaction to or deleting a reaction from 25 the data structure and repeating step (e), if the at least one flux distribution is predictive of a *Homo sapiens* physiological function, then storing the data structure in a computer readable medium or media. The invention further provides a data structure relating a 30 plurality of *Homo sapiens* reactants to a plurality of *Homo sapiens* reactions, wherein the data structure is produced by the method.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a schematic representation of a hypothetical metabolic network.

Figure 2 shows mass balance constraints and 5 flux constraints (reversibility constraints) that can be placed on the hypothetical metabolic network shown in Figure 1.

Figure 3 shows the stoichiometric matrix (S) for the hypothetical metabolic network shown in Figure 10 1.

Figure 4 shows, in Panel A, an exemplary biochemical reaction network and in Panel B, an exemplary regulatory control structure for the reaction network in panel A.

15

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides *in silico* models that describe the interconnections between genes in the *Homo sapiens* genome and their associated reactions and reactants. The models can be used to 20 simulate different aspects of the cellular behavior of human cells under different normal, pathological and therapeutic conditions, thereby providing valuable information for therapeutic, diagnostic and research applications. An advantage of the models of the 25 invention is that they provide a holistic approach to simulating and predicting the activity of *Homo sapiens* cells. The models and methods can also be extended to simulate the activity of multiple interacting cells,

including organs, physiological systems and whole body metabolism.

As an example, the *Homo sapiens* metabolic models of the invention can be used to determine the 5 effects of changes from aerobic to anaerobic conditions, such as occurs in skeletal muscles during exercise or in tumors, or to determine the effect of various dietary changes. The *Homo sapiens* metabolic models can also be used to determine the consequences 10 of genetic defects, such as deficiencies in metabolic enzymes such as phosphofructokinase, phosphoglycerate kinase, phosphoglycerate mutase, lactate dehydrogenase and adenosine deaminase.

The *Homo sapiens* metabolic models can also be 15 used to choose appropriate targets for drug design. Such targets include genes, proteins or reactants, which when modulated positively or negatively in a simulation produce a desired therapeutic result. The models and methods of the invention can also be used to 20 predict the effects of a therapeutic agent or dietary supplement on a cellular function of interest. Likewise, the models and methods can be used to predict both desirable and undesirable side effects of the therapeutic agent on an interrelated cellular function 25 in the target cell, as well as the desirable and undesirable effects that may occur in other cell types. Thus, the models and methods of the invention can make the drug development process more rapid and cost effective than is currently possible.

30 The *Homo sapiens* metabolic models can also be used to predict or validate the assignment of particular biochemical reactions to the enzyme-encoding genes found in the genome, and to identify the presence

of reactions or pathways not indicated by current genomic data. Thus, the models can be used to guide the research and discovery process, potentially leading to the identification of new enzymes, medicines or 5 metabolites of clinical importance.

The models of the invention are based on a data structure relating a plurality of *Homo sapiens* reactants to a plurality of *Homo sapiens* reactions, wherein each of the *Homo sapiens* reactions includes a 10 reactant identified as a substrate of the reaction, a reactant identified as a product of the reaction and a stoichiometric coefficient relating the substrate and the product. The reactions included in the data structure can be those that are common to all or most 15 *Homo sapiens* cells, such as core metabolic reactions, or reactions specific for one or more given cell type.

As used herein, the term "*Homo sapiens* reaction" is intended to mean a conversion that consumes a substrate or forms a product that occurs in 20 or by a *Homo sapiens* cell. The term can include a conversion that occurs due to the activity of one or more enzymes that are genetically encoded by a *Homo sapiens* genome. The term can also include a conversion that occurs spontaneously in a *Homo sapiens* cell. 25 Conversions included in the term include, for example, changes in chemical composition such as those due to nucleophilic or electrophilic addition, nucleophilic or electrophilic substitution, elimination, isomerization, deamination, phosphorylation, methylation, reduction, 30 oxidation or changes in location such as those that occur due to a transport reaction that moves a reactant from one cellular compartment to another. In the case of a transport reaction, the substrate and product of

the reaction can be chemically the same and the substrate and product can be differentiated according to location in a particular cellular compartment. Thus, a reaction that transports a chemically unchanged reactant from a first compartment to a second compartment has as its substrate the reactant in the first compartment and as its product the reactant in the second compartment. It will be understood that when used in reference to an *in silico* model or data structure, a reaction is intended to be a representation of a chemical conversion that consumes a substrate or produces a product.

As used herein, the term "*Homo sapiens* reactant" is intended to mean a chemical that is a substrate or a product of a reaction that occurs in or by a *Homo sapiens* cell. The term can include substrates or products of reactions performed by one or more enzymes encoded by a *Homo sapiens* genome, reactions occurring in *Homo sapiens* that are performed by one or more non-genetically encoded macromolecule, protein or enzyme, or reactions that occur spontaneously in a *Homo sapiens* cell. Metabolites are understood to be reactants within the meaning of the term. It will be understood that when used in reference to an *in silico* model or data structure, a reactant is intended to be a representation of a chemical that is a substrate or a product of a reaction that occurs in or by a *Homo sapiens* cell.

As used herein the term "substrate" is intended to mean a reactant that can be converted to one or more products by a reaction. The term can include, for example, a reactant that is to be chemically changed due to nucleophilic or electrophilic

addition, nucleophilic or electrophilic substitution, elimination, isomerization, deamination, phosphorylation, methylation, reduction, oxidation or that is to change location such as by being transported 5 across a membrane or to a different compartment.

As used herein, the term "product" is intended to mean a reactant that results from a reaction with one or more substrates. The term can include, for example, a reactant that has been 10 chemically changed due to nucleophilic or electrophilic addition, nucleophilic or electrophilic substitution, elimination, isomerization, deamination, phosphorylation, methylation, reduction or oxidation or that has changed location such as by being transported 15 across a membrane or to a different compartment.

As used herein, the term "stoichiometric coefficient" is intended to mean a numerical constant correlating the number of one or more reactants and the number of one or more products in a chemical reaction. 20 Typically, the numbers are integers as they denote the number of molecules of each reactant in an elementally balanced chemical equation that describes the corresponding conversion. However, in some cases the numbers can take on non-integer values, for example, 25 when used in a lumped reaction or to reflect empirical data.

As used herein, the term "plurality," when used in reference to *Homo sapiens* reactions or reactants, is intended to mean at least 2 reactions or 30 reactants. The term can include any number of *Homo sapiens* reactions or reactants in the range from 2 to the number of naturally occurring reactants or reactions for a particular of *Homo sapiens* cell. Thus,

the term can include, for example, at least 10, 20, 30, 50, 100, 150, 200, 300, 400, 500, 600 or more reactions or reactants. The number of reactions or reactants can be expressed as a portion of the total number of 5 naturally occurring reactions for a particular *Homo sapiens* cell, such as at least 20%, 30%, 50%, 60%, 75%, 90%, 95% or 98% of the total number of naturally occurring reactions that occur in a particular *Homo sapiens* cell.

10 As used herein, the term "data structure" is intended to mean a physical or logical relationship among data elements, designed to support specific data manipulation functions. The term can include, for example, a list of data elements that can be added 15 combined or otherwise manipulated such as a list of representations for reactions from which reactants can be related in a matrix or network. The term can also include a matrix that correlates data elements from two or more lists of information such as a matrix that 20 correlates reactants to reactions. Information included in the term can represent, for example, a substrate or product of a chemical reaction, a chemical reaction relating one or more substrates to one or more products, a constraint placed on a reaction, or a 25 stoichiometric coefficient.

As used herein, the term "constraint" is intended to mean an upper or lower boundary for a reaction. A boundary can specify a minimum or maximum flow of mass, electrons or energy through a reaction. 30 A boundary can further specify directionality of a reaction. A boundary can be a constant value such as zero, infinity, or a numerical value such as an integer. Alternatively, a boundary can be a variable boundary value as set forth below.

As used herein, the term "variable," when used in reference to a constraint is intended to mean capable of assuming any of a set of values in response to being acted upon by a constraint function. The term

5 "function," when used in the context of a constraint, is intended to be consistent with the meaning of the term as it is understood in the computer and mathematical arts. A function can be binary such that changes correspond to a reaction being off or on.

10 Alternatively, continuous functions can be used such that changes in boundary values correspond to increases or decreases in activity. Such increases or decreases can also be binned or effectively digitized by a function capable of converting sets of values to

15 discreet integer values. A function included in the term can correlate a boundary value with the presence, absence or amount of a biochemical reaction network participant such as a reactant, reaction, enzyme or gene. A function included in the term can correlate a

20 boundary value with an outcome of at least one reaction in a reaction network that includes the reaction that is constrained by the boundary limit. A function included in the term can also correlate a boundary value with an environmental condition such as time, pH,

25 temperature or redox potential.

As used herein, the term "activity," when used in reference to a reaction, is intended to mean the amount of product produced by the reaction, the amount of substrate consumed by the reaction or the

30 rate at which a product is produced or a substrate is consumed. The amount of product produced by the reaction, the amount of substrate consumed by the reaction or the rate at which a product is produced or a substrate is consumed can also be referred to as the

35 flux for the reaction.

As used herein, the term "activity," when used in reference to a *Homo sapiens* cell, is intended to mean the magnitude or rate of a change from an initial state to a final state. The term can include, 5 for example, the amount of a chemical consumed or produced by a cell, the rate at which a chemical is consumed or produced by a cell, the amount or rate of growth of a cell or the amount of or rate at which energy, mass or electrons flow through a particular 10 subset of reactions.

The invention provides a computer readable medium, having a data structure relating a plurality of *Homo sapiens* reactants to a plurality of *Homo sapiens* reactions, wherein each of the *Homo sapiens* reactions 15 includes a reactant identified as a substrate of the reaction, a reactant identified as a product of the reaction and a stoichiometric coefficient relating the substrate and the product.

Depending on the application, the plurality 20 of *Homo sapiens* reactions can include reactions selected from core metabolic reactions or peripheral metabolic reactions. As used herein, the term "core," when used in reference to a metabolic pathway, is intended to mean a metabolic pathway selected from 25 glycolysis/gluconeogenesis, the pentose phosphate pathway (PPP), the tricarboxylic acid (TCA) cycle, glycogen storage, electron transfer system (ETS), the malate/aspartate shuttle, the glycerol phosphate shuttle, and plasma and mitochondrial membrane 30 transporters. As used herein, the term "peripheral," when used in reference to a metabolic pathway, is intended to mean a metabolic pathway that includes one or more reactions that are not a part of a core metabolic pathway.

A plurality of *Homo sapiens* reactants can be related to a plurality of *Homo sapiens* reactions in any data structure that represents, for each reactant, the reactions by which it is consumed or produced. Thus, 5 the data structure, which is referred to herein as a "reaction network data structure," serves as a representation of a biological reaction network or system. An example of a reaction network that can be represented in a reaction network data structure of the 10 invention is the collection of reactions that constitute the core metabolic reactions of *Homo sapiens*, or the metabolic reactions of a skeletal muscle cell, as shown in the Examples.

The choice of reactions to include in a 15 particular reaction network data structure, from among all the possible reactions that can occur in human cells, depends on the cell type or types and the physiological, pathological or therapeutic condition being modeled, and can be determined experimentally or 20 from the literature, as described further below.

The reactions to be included in a particular network data structure of *Homo sapiens* can be determined experimentally using, for example, gene or protein expression profiles, where the molecular 25 characteristics of the cell can be correlated to the expression levels. The expression or lack of expression of genes or proteins in a cell type can be used in determining whether a reaction is included in the model by association to the expressed gene(s) and 30 or protein(s). Thus, it is possible to use experimental technologies to determine which genes and/or proteins are expressed in a specific cell type, and to further use this information to determine which reactions are present in the cell type of interest. In

this way a subset of reactions from all of those reactions that can occur in human cells are selected to comprise the set of reactions that represent a specific cell type. cDNA expression profiles have been 5 demonstrated to be useful, for example, for classification of breast cancer cells (Sorlie et al., Proc. Natl. Acad. Sci. U.S.A. 98(19):10869-10874 (2001)).

The methods and models of the invention can 10 be applied to any *Homo sapiens* cell type at any stage of differentiation, including, for example, embryonic stem cells, hematopoietic stem cells, differentiated hematopoietic cells, skeletal muscle cells, cardiac muscle cells, smooth muscle cells, skin cells, nerve 15 cells, kidney cells, pulmonary cells, liver cells, adipocytes and endocrine cells (e.g. beta islet cells of the pancreas, mammary gland cells, adrenal cells, and other specialized hormone secreting cells).

The methods and models of the invention can 20 be applied to normal cells or pathological cells. Normal cells that exhibit a variety of physiological activities of interest, including homeostasis, proliferation, differentiation, apoptosis, contraction and motility, can be modeled. Pathological cells can 25 also be modeled, including cells that reflect genetic or developmental abnormalities, nutritional deficiencies, environmental assaults, infection (such as by bacteria, viral, protozoan or fungal agents), neoplasia, aging, altered immune or endocrine function, 30 tissue damage, or any combination of these factors. The pathological cells can be representative of any type of human pathology, including, for example, various metabolic disorders of carbohydrate, lipid or protein metabolism, obesity, diabetes, cardiovascular

disease, fibrosis, various cancers, kidney failure, immune pathologies, neurodegenerative diseases, and various monogenetic metabolic diseases described in the Online Mendelian Inheritance in Man database (Center 5 for Medical Genetics, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine (Bethesda, MD)).

The methods and models of the invention can 10 also be applied to cells undergoing therapeutic perturbations, such as cells treated with drugs that target participants in a reaction network, cells treated with gene-based therapeutics that increase or decrease expression of an encoded protein, and cells 15 treated with radiation. As used herein, the term "drug" refers to a compound of any molecular nature with a known or proposed therapeutic function, including, for example, small molecule compounds, peptides and other macromolecules, peptidomimetics and 20 antibodies, any of which can optionally be tagged with cytostatic, targeting or detectable moieties. The term "gene-based therapeutic" refers to nucleic acid therapeutics, including, for example, expressible genes with normal or altered protein activity, antisense 25 compounds, ribozymes, DNAzymes, RNA interference compounds (RNAi) and the like. The therapeutics can target any reaction network participant, in any cellular location, including participants in extracellular, cell surface, cytoplasmic, mitochondrial 30 and nuclear locations. Experimental data that are gathered on the response of cells to therapeutic treatment, such as alterations in gene or protein expression profiles, can be used to tailor a network for a pathological state of a particular cell type.

The methods and models of the invention can be applied to *Homo sapiens* cells as they exist in any form, such as in primary cell isolates or in established cell lines, or in the whole body, in intact organs or in tissue explants. Accordingly, the methods and models can take into account intercellular communications and/or inter-organ communications, the effect of adhesion to a substrate or neighboring cells (such as a stem cell interacting with mesenchymal cells 10 or a cancer cell interacting with its tissue microenvironment, or beta-islet cells without normal stroma), and other interactions relevant to multicellular systems.

The reactants to be used in a reaction 15 network data structure of the invention can be obtained from or stored in a compound database. As used herein, the term "compound database" is intended to mean a computer readable medium or media containing a plurality of molecules that includes substrates and 20 products of biological reactions. The plurality of molecules can include molecules found in multiple organisms, thereby constituting a universal compound database. Alternatively, the plurality of molecules can be limited to those that occur in a particular 25 organism, thereby constituting an organism-specific compound database. Each reactant in a compound database can be identified according to the chemical species and the cellular compartment in which it is present. Thus, for example, a distinction can be made 30 between glucose in the extracellular compartment versus glucose in the cytosol. Additionally each of the reactants can be specified as a metabolite of a primary or secondary metabolic pathway. Although 35 identification of a reactant as a metabolite of a primary or secondary metabolic pathway does not

indicate any chemical distinction between the reactants in a reaction, such a designation can assist in visual representations of large networks of reactions.

As used herein, the term "compartment" is

5 intended to mean a subdivided region containing at least one reactant, such that the reactant is separated from at least one other reactant in a second region. A subdivided region included in the term can be correlated with a subdivided region of a cell. Thus, a

10 subdivided region included in the term can be, for example, the intracellular space of a cell; the extracellular space around a cell; the periplasmic space, the interior space of an organelle such as a mitochondrion, endoplasmic reticulum, Golgi apparatus,

15 vacuole or nucleus; or any subcellular space that is separated from another by a membrane or other physical barrier. Subdivided regions can also be made in order to create virtual boundaries in a reaction network that are not correlated with physical barriers. Virtual

20 boundaries can be made for the purpose of segmenting the reactions in a network into different compartments or substructures.

As used herein, the term "substructure" is intended to mean a portion of the information in a data

25 structure that is separated from other information in the data structure such that the portion of information can be separately manipulated or analyzed. The term can include portions subdivided according to a biological function including, for example, information

30 relevant to a particular metabolic pathway such as an internal flux pathway, exchange flux pathway, central metabolic pathway, peripheral metabolic pathway, or secondary metabolic pathway. The term can include portions subdivided according to computational or

mathematical principles that allow for a particular type of analysis or manipulation of the data structure.

The reactions included in a reaction network data structure can be obtained from a metabolic 5 reaction database that includes the substrates, products, and stoichiometry of a plurality of metabolic reactions of *Homo sapiens*. The reactants in a reaction network data structure can be designated as either substrates or products of a particular reaction, each 10 with a stoichiometric coefficient assigned to it to describe the chemical conversion taking place in the reaction. Each reaction is also described as occurring in either a reversible or irreversible direction.

Reversible reactions can either be represented as one 15 reaction that operates in both the forward and reverse direction or be decomposed into two irreversible reactions, one corresponding to the forward reaction and the other corresponding to the backward reaction.

Reactions included in a reaction network data 20 structure can include intra-system or exchange reactions. Intra-system reactions are the chemically and electrically balanced interconversions of chemical species and transport processes, which serve to replenish or drain the relative amounts of certain 25 metabolites. These intra-system reactions can be classified as either being transformations or translocations. A transformation is a reaction that contains distinct sets of compounds as substrates and products, while a translocation contains reactants 30 located in different compartments. Thus a reaction that simply transports a metabolite from the extracellular environment to the cytosol, without changing its chemical composition is solely classified as a translocation, while a reaction that takes an

extracellular substrate and converts it into a cytosolic product is both a translocation and a transformation.

Exchange reactions are those which constitute sources and sinks, allowing the passage of metabolites into and out of a compartment or across a hypothetical system boundary. These reactions are included in a model for simulation purposes and represent the metabolic demands placed on *Homo sapiens*. While they may be chemically balanced in certain cases, they are typically not balanced and can often have only a single substrate or product. As a matter of convention the exchange reactions are further classified into demand exchange and input/output exchange reactions.

15           The metabolic demands placed on the *Homo sapiens* metabolic reaction network can be readily determined from the dry weight composition of the cell which is available in the published literature or which can be determined experimentally. The uptake rates and 20 maintenance requirements for *Homo sapiens* cells can also be obtained from the published literature or determined experimentally.

Input/output exchange reactions are used to allow extracellular reactants to enter or exit the 25 reaction network represented by a model of the invention. For each of the extracellular metabolites a corresponding input/output exchange reaction can be created. These reactions are always reversible with the metabolite indicated as a substrate with a 30 stoichiometric coefficient of one and no products produced by the reaction. This particular convention is adopted to allow the reaction to take on a positive flux value (activity level) when the metabolite is

being produced or removed from the reaction network and a negative flux value when the metabolite is being consumed or introduced into the reaction network. These reactions will be further constrained during the 5 course of a simulation to specify exactly which metabolites are available to the cell and which can be excreted by the cell.

A demand exchange reaction is always specified as an irreversible reaction containing at 10 least one substrate. These reactions are typically formulated to represent the production of an intracellular metabolite by the metabolic network or the aggregate production of many reactants in balanced ratios such as in the representation of a reaction that 15 leads to biomass formation, also referred to as growth.

A demand exchange reactions can be introduced for any metabolite in a model of the invention. Most commonly these reactions are introduced for metabolites that are required to be produced by the cell for the 20 purposes of creating a new cell such as amino acids, nucleotides, phospholipids, and other biomass constituents, or metabolites that are to be produced for alternative purposes. Once these metabolites are identified, a demand exchange reaction that is 25 irreversible and specifies the metabolite as a substrate with a stoichiometric coefficient of unity can be created. With these specifications, if the reaction is active it leads to the net production of the metabolite by the system meeting potential 30 production demands. Examples of processes that can be represented as a demand exchange reaction in a reaction network data structure and analyzed by the methods of the invention include, for example, production or secretion of an individual protein; production or

secretion of an individual metabolite such as an amino acid, vitamin, nucleoside, antibiotic or surfactant; production of ATP for extraneous energy requiring processes such as locomotion; or formation of biomass

5 constituents.

In addition to these demand exchange reactions that are placed on individual metabolites, demand exchange reactions that utilize multiple metabolites in defined stoichiometric ratios can be

10 introduced. These reactions are referred to as aggregate demand exchange reactions. An example of an aggregate demand reaction is a reaction used to simulate the concurrent growth demands or production requirements associated with cell growth that are

15 placed on a cell, for example, by simulating the formation of multiple biomass constituents simultaneously at a particular cellular growth rate.

A hypothetical reaction network is provided in Figure 1 to exemplify the above-described reactions and their interactions. The reactions can be

20 represented in the exemplary data structure shown in Figure 3 as set forth below. The reaction network, shown in Figure 1, includes intrasystem reactions that occur entirely within the compartment indicated by the

25 shaded oval such as reversible reaction  $R_2$  which acts on reactants B and G and reaction  $R_3$  which converts one equivalent of B to 2 equivalents of F. The reaction network shown in Figure 1 also contains exchange reactions such as input/output exchange reactions  $A_{xt}$

30 and  $E_{xt}$ , and the demand exchange reaction,  $V_{growth}$ , which represents growth in response to the one equivalent of D and one equivalent of F. Other intrasystem reactions include  $R_1$  which is a translocation and transformation reaction that translocates reactant A into the

compartment and transforms it to reactant G and reaction  $R_6$  which is a transport reaction that translocates reactant E out of the compartment.

A reaction network can be represented as a 5 set of linear algebraic equations which can be presented as a stoichiometric matrix S, with S being an  $m \times n$  matrix where m corresponds to the number of reactants or metabolites and n corresponds to the 10 number of reactions taking place in the network. An example of a stoichiometric matrix representing the reaction network of Figure 1 is shown in Figure 3. As shown in Figure 3, each column in the matrix corresponds to a particular reaction n, each row corresponds to a particular reactant m, and each  $S_{mn}$  15 element corresponds to the stoichiometric coefficient of the reactant m in the reaction denoted n. The stoichiometric matrix includes intra-system reactions such as  $R_2$  and  $R_3$  which are related to reactants that participate in the respective reactions according to a 20 stoichiometric coefficient having a sign indicative of whether the reactant is a substrate or product of the reaction and a value correlated with the number of equivalents of the reactant consumed or produced by the reaction. Exchange reactions such as  $-E_{xt}$  and  $-A_{xt}$  are 25 similarly correlated with a stoichiometric coefficient. As exemplified by reactant E, the same compound can be treated separately as an internal reactant (E) and an external reactant ( $E_{external}$ ) such that an exchange reaction ( $R_6$ ) exporting the compound is correlated by 30 stoichiometric coefficients of -1 and 1, respectively. However, because the compound is treated as a separate reactant by virtue of its compartmental location, a reaction, such as  $R_5$ , which produces the internal reactant (E) but does not act on the external reactant 35 ( $E_{external}$ ) is correlated by stoichiometric coefficients

of 1 and 0, respectively. Demand reactions such as  $V_{growth}$  can also be included in the stoichiometric matrix being correlated with substrates by an appropriate stoichiometric coefficient.

5

As set forth in further detail below, a stoichiometric matrix provides a convenient format for representing and analyzing a reaction network because it can be readily manipulated and used to compute 10 network properties, for example, by using linear programming or general convex analysis. A reaction network data structure can take on a variety of formats so long as it is capable of relating reactants and reactions in the manner exemplified above for a 15 stoichiometric matrix and in a manner that can be manipulated to determine an activity of one or more reactions using methods such as those exemplified below. Other examples of reaction network data structures that are useful in the invention include a 20 connected graph, list of chemical reactions or a table of reaction equations.

A reaction network data structure can be constructed to include all reactions that are involved 25 in *Homo sapiens* metabolism or any portion thereof. A portion of *Homo sapiens* metabolic reactions that can be included in a reaction network data structure of the invention includes, for example, a central metabolic pathway such as glycolysis, the TCA cycle, the PPP or 30 ETS; or a peripheral metabolic pathway such as amino acid biosynthesis, amino acid degradation, purine biosynthesis, pyrimidine biosynthesis, lipid biosynthesis, fatty acid metabolism, vitamin or cofactor biosynthesis, transport processes and 35 alternative carbon source catabolism. Examples of

individual pathways within the peripheral pathways are set forth in Table 1.

Depending upon a particular application, a reaction network data structure can include a plurality 5 of *Homo sapiens* reactions including any or all of the reactions listed in Table 1.

For some applications, it can be advantageous to use a reaction network data structure that includes a minimal number of reactions to achieve a particular 10 *Homo sapiens* activity under a particular set of environmental conditions. A reaction network data structure having a minimal number of reactions can be identified by performing the simulation methods described below in an iterative fashion where different 15 reactions or sets of reactions are systematically removed and the effects observed. Accordingly, the invention provides a computer readable medium, containing a data structure relating a plurality of *Homo sapiens* reactants to a plurality of *Homo sapiens* 20 reactions, wherein the plurality of *Homo sapiens* reactions contains at least 65 reactions. For example, the core metabolic reaction database shown in Tables 2 and 3 contains 65 reactions, and is sufficient to simulate aerobic and anaerobic metabolism on a number 25 of carbon sources, including glucose.

Depending upon the particular cell type or types, the physiological, pathological or therapeutic conditions being tested and the desired activity, a reaction network data structure can contain smaller 30 numbers of reactions such as at least 200, 150, 100 or 50 reactions. A reaction network data structure having relatively few reactions can provide the advantage of reducing computation time and resources required to

perform a simulation. When desired, a reaction network data structure having a particular subset of reactions can be made or used in which reactions that are not relevant to the particular simulation are omitted.

5 Alternatively, larger numbers of reactions can be included in order to increase the accuracy or molecular detail of the methods of the invention or to suit a particular application. Thus, a reaction network data structure can contain at least 300, 350, 400, 450, 500,  
10 550, 600 or more reactions up to the number of reactions that occur in or by *Homo sapiens* or that are desired to simulate the activity of the full set of reactions occurring in *Homo sapiens*. A reaction network data structure that is substantially complete  
15 with respect to the metabolic reactions of *Homo sapiens* provides the advantage of being relevant to a wide range of conditions to be simulated, whereas those with smaller numbers of metabolic reactions are limited to a particular subset of conditions to be simulated.

20 A *Homo sapiens* reaction network data structure can include one or more reactions that occur in or by *Homo sapiens* and that do not occur, either naturally or following manipulation, in or by another organism, such as *Saccharomyces cerevisiae*. It is  
25 understood that a *Homo sapiens* reaction network data structure of a particular cell type can also include one or more reactions that occur in another cell type. Addition of such heterologous reactions to a reaction network data structure of the invention can be used in  
30 methods to predict the consequences of heterologous gene transfer and protein expression, for example, when designing *in vivo* and *ex vivo* gene therapy approaches.

The reactions included in a reaction network data structure of the invention can be metabolic reactions. A reaction network data structure can also be constructed to include other types of reactions such 5 as regulatory reactions, signal transduction reactions, cell cycle reactions, reactions controlling developmental processes, reactions involved in apoptosis, reactions involved in responses to hypoxia, reactions involved in responses to cell-cell or cell- 10 substrate interactions, reactions involved in protein synthesis and regulation thereof, reactions involved in gene transcription and translation, and regulation thereof, and reactions involved in assembly of a cell and its subcellular components.

15 A reaction network data structure or index of reactions used in the data structure such as that available in a metabolic reaction database, as described above, can be annotated to include information about a particular reaction. A reaction 20 can be annotated to indicate, for example, assignment of the reaction to a protein, macromolecule or enzyme that performs the reaction, assignment of a gene(s) that codes for the protein, macromolecule or enzyme, the Enzyme Commission (EC) number of the particular 25 metabolic reaction, a subset of reactions to which the reaction belongs, citations to references from which information was obtained, or a level of confidence with which a reaction is believed to occur in *Homo sapiens*. A computer readable medium or media of the invention 30 can include a gene database containing annotated reactions. Such information can be obtained during the course of building a metabolic reaction database or model of the invention as described below.

As used herein, the term "gene database" is intended to mean a computer readable medium or media that contains at least one reaction that is annotated to assign a reaction to one or more macromolecules that

5 perform the reaction or to assign one or more nucleic acid that encodes the one or more macromolecules that perform the reaction. A gene database can contain a plurality of reactions, some or all of which are annotated. An annotation can include, for example, a

10 name for a macromolecule; assignment of a function to a macromolecule; assignment of an organism that contains the macromolecule or produces the macromolecule; assignment of a subcellular location for the macromolecule; assignment of conditions under which a

15 macromolecule is regulated with respect to performing a reaction, being expressed or being degraded; assignment of a cellular component that regulates a macromolecule; an amino acid or nucleotide sequence for the macromolecule; or any other annotation found for a

20 macromolecule in a genome database such as those that can be found in Genbank, a site maintained by the NCBI ([ncbi.nlm.gov](http://ncbi.nlm.gov)), the Kyoto Encyclopedia of Genes and Genomes (KEGG) ([www.genome.ad.jp/kegg/](http://www.genome.ad.jp/kegg/)), the protein database SWISS-PROT ([ca.expasy.org/sprot/](http://ca.expasy.org/sprot/)), the

25 LocusLink database maintained by the NCBI ([www.ncbi.nlm.nih.gov/LocusLink/](http://www.ncbi.nlm.nih.gov/LocusLink/)), the Enzyme Nomenclature database maintained by G.P. Moss of Queen Mary and Westfield College in the United Kingdom ([www.chem.qmw.ac.uk/iubmb/enzyme/](http://www.chem.qmw.ac.uk/iubmb/enzyme/)).

30 A gene database of the invention can include a substantially complete collection of genes or open reading frames in *Homo sapiens* or a substantially complete collection of the macromolecules encoded by the *Homo sapiens* genome. Alternatively, a gene

35 database can include a portion of genes or open reading

frames in *Homo sapiens* or a portion of the macromolecules encoded by the *Homo sapiens* genome, such as the portion that includes substantially all metabolic genes or macromolecules. The portion can be 5 at least 10%, 15%, 20%, 25%, 50%, 75%, 90% or 95% of the genes or open reading frames encoded by the *Homo sapiens* genome, or the macromolecules encoded therein. A gene database can also include macromolecules encoded by at least a portion of the nucleotide sequence for 10 the *Homo sapiens* genome such as at least 10%, 15%, 20%, 25%, 50%, 75%, 90% or 95% of the *Homo sapiens* genome. Accordingly, a computer readable medium or media of the invention can include at least one reaction for each 15 macromolecule encoded by a portion of the *Homo sapiens* genome.

An *in silico* *Homo sapiens* model of the invention can be built by an iterative process which includes gathering information regarding particular reactions to be added to a model, representing the 20 reactions in a reaction network data structure, and performing preliminary simulations wherein a set of constraints is placed on the reaction network and the output evaluated to identify errors in the network. Errors in the network such as gaps that lead to non- 25 natural accumulation or consumption of a particular metabolite can be identified as described below and simulations repeated until a desired performance of the model is attained. An exemplary method for iterative model construction is provided in Example I.

30 Thus, the invention provides a method for making a data structure relating a plurality of *Homo sapiens* reactants to a plurality of *Homo sapiens* reactions in a computer readable medium or media. The

method includes the steps of: (a) identifying a plurality of *Homo sapiens* reactions and a plurality of *Homo sapiens* reactants that are substrates and products of the *Homo sapiens* reactions; (b) relating the 5 plurality of *Homo sapiens* reactants to the plurality of *Homo sapiens* reactions in a data structure, wherein each of the *Homo sapiens* reactions includes a reactant identified as a substrate of the reaction, a reactant identified as a product of the reaction and a 10 stoichiometric coefficient relating the substrate and the product; (c) making a constraint set for the plurality of *Homo sapiens* reactions; (d) providing an objective function; (e) determining at least one flux distribution that minimizes or maximizes the objective 15 function when the constraint set is applied to the data structure, and (f) if the at least one flux distribution is not predictive of *Homo sapiens* physiology, then adding a reaction to or deleting a reaction from the data structure and repeating step 20 (e), if the at least one flux distribution is predictive of *Homo sapiens* physiology, then storing the data structure in a computer readable medium or media.

Information to be included in a data structure of the invention can be gathered from a 25 variety of sources including, for example, annotated genome sequence information and biochemical literature.

Sources of annotated human genome sequence information include, for example, KEGG, SWISS-PROT, LocusLink, the Enzyme Nomenclature database, the 30 International Human Genome Sequencing Consortium and commercial databases. KEGG contains a broad range of information, including a substantial amount of metabolic reconstruction. The genomes of 63 organisms

can be accessed here, with gene products grouped by coordinated functions, often represented by a map (e.g., the enzymes involved in glycolysis would be grouped together). The maps are biochemical pathway 5 templates which show enzymes connecting metabolites for various parts of metabolism. These general pathway templates are customized for a given organism by highlighting enzymes on a given template which have been identified in the genome of the organism. Enzymes 10 and metabolites are active and yield useful information about stoichiometry, structure, alternative names and the like, when accessed.

SWISS-PROT contains detailed information about protein function. Accessible information 15 includes alternate gene and gene product names, function, structure and sequence information, relevant literature references, and the like.

LocusLink contains general information about the locus where the gene is located and, of relevance, 20 tissue specificity, cellular location, and implication of the gene product in various disease states.

The Enzyme Nomenclature database can be used to compare the gene products of two organisms. Often the gene names for genes with similar functions in two 25 or more organisms are unrelated. When this is the case, the E.C. (Enzyme Commission) numbers can be used as unambiguous indicators of gene product function. The information in the Enzyme Nomenclature database is also published in Enzyme Nomenclature (Academic Press, 30 San Diego, California, 1992) with 5 supplements to date, all found in the European Journal of Biochemistry (Blackwell Science, Malden, MA).

Sources of biochemical information include, for example, general resources relating to metabolism, resources relating specifically to human metabolism, and resources relating to the biochemistry, physiology and pathology of specific human cell types.

Sources of general information relating to metabolism, which were used to generate the human reaction databases and models described herein, were J.G. Salway, Metabolism at a Glance, 2<sup>nd</sup> ed., Blackwell Science, Malden, MA (1999) and T.M. Devlin, ed., Textbook of Biochemistry with Clinical Correlations, 4<sup>th</sup> ed., John Wiley and Sons, New York, NY (1997). Human metabolism-specific resources included J.R. Bronk, Human Metabolism: Functional Diversity and Integration, Addison Wesley Longman, Essex, England (1999).

The literature used in conjunction with the skeletal muscle metabolic models and simulations described herein included R. Maughan et al., 20 Biochemistry of Exercise and Training, Oxford University Press, Oxford, England (1997), as well as references on muscle pathology such as S. Carpenter et al., Pathology of Skeletal Muscle, 2<sup>nd</sup> ed., Oxford University Press, Oxford, England (2001), and more 25 specific articles on muscle metabolism as may be found in the *Journal of Physiology* (Cambridge University Press, Cambridge, England).

In the course of developing an *in silico* 30 model of *Homo sapiens* metabolism, the types of data that can be considered include, for example, biochemical information which is information related to the experimental characterization of a chemical reaction, often directly indicating a protein(s)

associated with a reaction and the stoichiometry of the reaction or indirectly demonstrating the existence of a reaction occurring within a cellular extract; genetic information, which is information related to the

5 experimental identification and genetic characterization of a gene(s) shown to code for a particular protein(s) implicated in carrying out a biochemical event; genomic information, which is information related to the identification of an open

10 reading frame and functional assignment, through computational sequence analysis, that is then linked to a protein performing a biochemical event; physiological information, which is information related to overall cellular physiology, fitness characteristics, substrate

15 utilization, and phenotyping results, which provide evidence of the assimilation or dissimilation of a compound used to infer the presence of specific biochemical event (in particular translocations); and modeling information, which is information generated

20 through the course of simulating activity of *Homo sapiens* cells using methods such as those described herein which lead to predictions regarding the status of a reaction such as whether or not the reaction is required to fulfill certain demands placed on a

25 metabolic network. Additional information relevant to multicellular organisms that can be considered includes cell type-specific or condition-specific gene expression information, which can be determined experimentally, such as by gene array analysis or from

30 expressed sequence tag (EST) analysis, or obtained from the biochemical and physiological literature.

The majority of the reactions occurring in *Homo sapiens* reaction networks are catalyzed by enzymes/proteins, which are created through the

35 transcription and translation of the genes found within

the chromosome in the cell. The remaining reactions occur either spontaneously or through non-enzymatic processes. Furthermore, a reaction network data structure can contain reactions that add or delete 5 steps to or from a particular reaction pathway. For example, reactions can be added to optimize or improve performance of a *Homo sapiens* model in view of empirically observed activity. Alternatively, reactions can be deleted to remove intermediate steps 10 in a pathway when the intermediate steps are not necessary to model flux through the pathway. For example, if a pathway contains 3 nonbranched steps, the reactions can be combined or added together to give a net reaction, thereby reducing memory required to store 15 the reaction network data structure and the computational resources required for manipulation of the data structure.

The reactions that occur due to the activity of gene-encoded enzymes can be obtained from a genome 20 database which lists genes identified from genome sequencing and subsequent genome annotation. Genome annotation consists of the locations of open reading frames and assignment of function from homology to other known genes or empirically determined activity. 25 Such a genome database can be acquired through public or private databases containing annotated *Homo sapiens* nucleic acid or protein sequences. If desired, a model developer can perform a network reconstruction and establish the model content associations between the 30 genes, proteins, and reactions as described, for example, in Covert et al. Trends in Biochemical Sciences 26:179-186 (2001) and Palsson, WO 00/46405.

As reactions are added to a reaction network 35 data structure or metabolic reaction database, those

having known or putative associations to the proteins/enzymes which enable/catalyze the reaction and the associated genes that code for these proteins can be identified by annotation. Accordingly, the 5 appropriate associations for all of the reactions to their related proteins or genes or both can be assigned. These associations can be used to capture the non-linear relationship between the genes and proteins as well as between proteins and reactions. In 10 some cases one gene codes for one protein which then perform one reaction. However, often there are multiple genes which are required to create an active enzyme complex and often there are multiple reactions that can be carried out by one protein or multiple 15 proteins that can carry out the same reaction. These associations capture the logic (i.e. AND or OR relationships) within the associations. Annotating a metabolic reaction database with these associations can allow the methods to be used to determine the effects 20 of adding or eliminating a particular reaction not only at the reaction level, but at the genetic or protein level in the context of running a simulation or predicting *Homo sapiens* activity.

A reaction network data structure of the 25 invention can be used to determine the activity of one or more reactions in a plurality of *Homo sapiens* reactions independent of any knowledge or annotation of the identity of the protein that performs the reaction or the gene encoding the protein. A model that is 30 annotated with gene or protein identities can include reactions for which a protein or encoding gene is not assigned. While a large portion of the reactions in a cellular metabolic network are associated with genes in the organism's genome, there are also a substantial 35 number of reactions included in a model for which there

are no known genetic associations. Such reactions can be added to a reaction database based upon other information that is not necessarily related to genetics such as biochemical or cell based measurements or

5     theoretical considerations based on observed biochemical or cellular activity. For example, there are many reactions that can either occur spontaneously or are not protein-enabled reactions. Furthermore, the occurrence of a particular reaction in a cell for which

10    no associated proteins or genetics have been currently identified can be indicated during the course of model building by the iterative model building methods of the invention.

The reactions in a reaction network data

15    structure or reaction database can be assigned to subsystems by annotation, if desired. The reactions can be subdivided according to biological criteria, such as according to traditionally identified metabolic pathways (glycolysis, amino acid metabolism and the

20    like) or according to mathematical or computational criteria that facilitate manipulation of a model that incorporates or manipulates the reactions. Methods and criteria for subdividing a reaction database are described in further detail in Schilling et al., J.

25    Theor. Biol. 203:249-283 (2000), and in Schuster et al., Bioinformatics 18:351-361 (2002). The use of subsystems can be advantageous for a number of analysis methods, such as extreme pathway analysis, and can make the management of model content easier. Although

30    assigning reactions to subsystems can be achieved without affecting the use of the entire model for simulation, assigning reactions to subsystems can allow a user to search for reactions in a particular subsystem which may be useful in performing various

35    types of analyses. Therefore, a reaction network data

structure can include any number of desired subsystems including, for example, 2 or more subsystems, 5 or more subsystems, 10 or more subsystems, 25 or more subsystems or 50 or more subsystems.

5        The reactions in a reaction network data structure or metabolic reaction database can be annotated with a value indicating the confidence with which the reaction is believed to occur in the *Homo sapiens* cell. The level of confidence can be, for  
10      example, a function of the amount and form of supporting data that is available. This data can come in various forms including published literature, documented experimental results, or results of computational analyses. Furthermore, the data can  
15      provide direct or indirect evidence for the existence of a chemical reaction in a cell based on genetic, biochemical, and/or physiological data.

          The invention further provides a computer readable medium, containing (a) a data structure  
20      relating a plurality of *Homo sapiens* reactants to a plurality of *Homo sapiens* reactions, wherein each of the *Homo sapiens* reactions includes a reactant identified as a substrate of the reaction, a reactant identified as a product of the reaction and a  
25      stoichiometric coefficient relating the substrate and the product, and (b) a constraint set for the plurality of *Homo sapiens* reactions.

          Constraints can be placed on the value of any of the fluxes in the metabolic network using a  
30      constraint set. These constraints can be representative of a minimum or maximum allowable flux through a given reaction, possibly resulting from a limited amount of an enzyme present. Additionally, the

constraints can determine the direction or reversibility of any of the reactions or transport fluxes in the reaction network data structure. Based on the *in vivo* environment where *Homo sapiens* lives the 5 metabolic resources available to the cell for biosynthesis of essential molecules for can be determined. Allowing the corresponding transport fluxes to be active provides the *in silico* *Homo sapiens* with inputs and outputs for substrates and by-products 10 produced by the metabolic network.

Returning to the hypothetical reaction network shown in Figure 1, constraints can be placed on each reaction in the exemplary format shown in Figure 2, as follows. The constraints are provided in a 15 format that can be used to constrain the reactions of the stoichiometric matrix shown in Figure 3. The format for the constraints used for a matrix or in linear programming can be conveniently represented as a linear inequality such as

$$20 \quad b_j \leq v_j \leq a_j : j = 1 \dots n \quad (\text{Eq. 1})$$

where  $v_j$  is the metabolic flux vector,  $b_j$  is the minimum flux value and  $a_j$  is the maximum flux value. Thus,  $a_j$  can take on a finite value representing a maximum allowable flux through a given reaction or  $b_j$  25 can take on a finite value representing minimum allowable flux through a given reaction. Additionally, if one chooses to leave certain reversible reactions or transport fluxes to operate in a forward and reverse manner the flux may remain unconstrained by setting  $b_j$  30 to negative infinity and  $a_j$  to positive infinity as shown for reaction  $R_2$  in Figure 2. If reactions proceed only in the forward reaction  $b_j$  is set to zero while  $a_j$  is set to positive infinity as shown for

reactions  $R_1$ ,  $R_3$ ,  $R_4$ ,  $R_5$ , and  $R_6$  in Figure 2. As an example, to simulate the event of a genetic deletion or non-expression of a particular protein, the flux through all of the corresponding metabolic reactions related to the gene or protein in question are reduced to zero by setting  $a_j$  and  $b_j$  to be zero. Furthermore, if one wishes to simulate the absence of a particular growth substrate one can simply constrain the corresponding transport fluxes that allow the metabolite to enter the cell to be zero by setting  $a_j$  and  $b_j$  to be zero. On the other hand if a substrate is only allowed to enter or exit the cell via transport mechanisms, the corresponding fluxes can be properly constrained to reflect this scenario.

The ability of a reaction to be actively occurring is dependent on a large number of additional factors beyond just the availability of substrates. These factors, which can be represented as variable constraints in the models and methods of the invention include, for example, the presence of cofactors necessary to stabilize the protein/enzyme, the presence or absence of enzymatic inhibition and activation factors, the active formation of the protein/enzyme through translation of the corresponding mRNA transcript, the transcription of the associated gene(s) or the presence of chemical signals and/or proteins that assist in controlling these processes that ultimately determine whether a chemical reaction is capable of being carried out within an organism. Of particular importance in the regulation of human cell types is the implementation of paracrine and endocrine signaling pathways to control cellular activities. In these cases a cell secretes signaling molecules that may be carried far afield to act on distant targets (endocrine signaling), or act as local mediators

(paracrine signaling). Examples of endocrine signaling molecules include hormones such as insulin, while examples of paracrine signaling molecules include neurotransmitters such as acetylcholine. These 5 molecules induce cellular responses through signaling cascades that affect the activity of biochemical reactions in the cell. Regulation can be represented in an *in silico* *Homo sapiens* model by providing a variable constraint as set forth below.

10

Thus, the invention provides a computer readable medium or media, including (a) a data structure relating a plurality of *Homo sapiens* reactants to a plurality of *Homo sapiens* reactions, 15 wherein each of the reactions includes a reactant identified as a substrate of the reaction, a reactant identified as a product of the reaction and a stoichiometric coefficient relating the substrate and the product, and wherein at least one of the reactions 20 is a regulated reaction; and (b) a constraint set for the plurality of reactions, wherein the constraint set includes a variable constraint for the regulated reaction.

As used herein, the term "regulated," when 25 used in reference to a reaction in a data structure, is intended to mean a reaction that experiences an altered flux due to a change in the value of a constraint or a reaction that has a variable constraint.

As used herein, the term "regulatory 30 reaction" is intended to mean a chemical conversion or interaction that alters the activity of a protein, macromolecule or enzyme. A chemical conversion or interaction can directly alter the activity of a protein, macromolecule or enzyme such as occurs when

the protein, macromolecule or enzyme is post-translationally modified or can indirectly alter the activity of a protein, macromolecule or enzyme such as occurs when a chemical conversion or binding event 5 leads to altered expression of the protein, macromolecule or enzyme. Thus, transcriptional or translational regulatory pathways can indirectly alter a protein, macromolecule or enzyme or an associated reaction. Similarly, indirect regulatory reactions can 10 include reactions that occur due to downstream components or participants in a regulatory reaction network. When used in reference to a data structure or *in silico Homo sapiens* model, the term is intended to mean a first reaction that is related to a second 15 reaction by a function that alters the flux through the second reaction by changing the value of a constraint on the second reaction.

As used herein, the term "regulatory data structure" is intended to mean a representation of an 20 event, reaction or network of reactions that activate or inhibit a reaction, the representation being in a format that can be manipulated or analyzed. An event that activates a reaction can be an event that initiates the reaction or an event that increases the 25 rate or level of activity for the reaction. An event that inhibits a reaction can be an event that stops the reaction or an event that decreases the rate or level of activity for the reaction. Reactions that can be represented in a regulatory data structure include, for 30 example, reactions that control expression of a macromolecule that in turn, performs a reaction such as transcription and translation reactions, reactions that lead to post translational modification of a protein or enzyme such as phosphorylation, dephosphorylation, 35 prenylation, methylation, oxidation or covalent

modification, reactions that process a protein or enzyme such as removal of a pre- or pro-sequence, reactions that degrade a protein or enzyme or reactions that lead to assembly of a protein or enzyme.

5 As used herein, the term "regulatory event" is intended to mean a modifier of the flux through a reaction that is independent of the amount of reactants available to the reaction. A modification included in the term can be a change in the presence, absence, or  
10 amount of an enzyme that performs a reaction. A modifier included in the term can be a regulatory reaction such as a signal transduction reaction or an environmental condition such as a change in pH, temperature, redox potential or time. It will be  
15 understood that when used in reference to an *in silico* *Homo sapiens* model or data structure a regulatory event is intended to be a representation of a modifier of the flux through a *Homo sapiens* reaction that is independent of the amount of reactants available to the  
20 reaction.

The effects of regulation on one or more reactions that occur in *Homo sapiens* can be predicted using an *in silico* *Homo sapiens* model of the invention.  
25 Regulation can be taken into consideration in the context of a particular condition being examined by providing a variable constraint for the reaction in an *in silico* *Homo sapiens* model. Such constraints constitute condition-dependent constraints. A data  
30 structure can represent regulatory reactions as Boolean logic statements (Reg-reaction). The variable takes on a value of 1 when the reaction is available for use in the reaction network and will take on a value of 0 if the reaction is restrained due to some regulatory  
35 feature. A series of Boolean statements can then be

introduced to mathematically represent the regulatory network as described for example in Covert et al. J. Theor. Biol. 213:73-88 (2001). For example, in the case of a transport reaction ( $A_{in}$ ) that imports 5 metabolite A, where metabolite A inhibits reaction R2 as shown in Figure 4, a Boolean rule can state that:

$$\text{Reg-R2} = \text{IF NOT}(A_{in}). \quad (\text{Eq. 2})$$

This statement indicates that reaction R2 can occur if 10 reaction  $A_{in}$  is not occurring (i.e. if metabolite A is not present). Similarly, it is possible to assign the regulation to a variable A which would indicate an amount of A above or below a threshold that leads to the inhibition of reaction R2. Any function that 15 provides values for variables corresponding to each of the reactions in the biochemical reaction network can be used to represent a regulatory reaction or set of regulatory reactions in a regulatory data structure. Such functions can include, for example, fuzzy logic, 20 heuristic rule-based descriptions, differential equations or kinetic equations detailing system dynamics.

A reaction constraint placed on a reaction can be incorporated into an *in silico Homo sapiens* 25 model using the following general equation:

$$\begin{aligned} & (\text{Reg-Reaction}) * b_j \leq v_j \leq a_j * (\text{Reg-Reaction}) \\ & : (\text{Eq. 3}) \\ & j = 1....n \end{aligned}$$

For the example of reaction R2 this equation is written 30 as follows:

$$(0) * \text{Reg-R2} \leq R2 \leq (\infty) * \text{Reg-R2}. \quad (\text{Eq. 4})$$

Thus, during the course of a simulation, depending upon the presence or absence of metabolite A in the interior of the cell where reaction R2 occurs, the value for the upper boundary of flux for reaction R2 will change from 5 0 to infinity, respectively.

With the effects of a regulatory event or network taken into consideration by a constraint function and the condition-dependent constraints set to an initial relevant value, the behavior of the *Homo sapiens* reaction network can be simulated for the 10 conditions considered as set forth below.

Although regulation has been exemplified above for the case where a variable constraint is dependent upon the outcome of a reaction in the data 15 structure, a plurality of variable constraints can be included in an *in silico Homo sapiens* model to represent regulation of a plurality of reactions. Furthermore, in the exemplary case set forth above, the regulatory structure includes a general control stating 20 that a reaction is inhibited by a particular environmental condition. Using a general control of this type, it is possible to incorporate molecular mechanisms and additional detail into the regulatory structure that is responsible for determining the 25 active nature of a particular chemical reaction within an organism.

Regulation can also be simulated by a model of the invention and used to predict a *Homo sapiens* physiological function without knowledge of the precise 30 molecular mechanisms involved in the reaction network being modeled. Thus, the model can be used to predict, *in silico*, overall regulatory events or causal relationships that are not apparent from *in vivo*

observation of any one reaction in a network or whose in vivo effects on a particular reaction are not known. Such overall regulatory effects can include those that result from overall environmental conditions such as 5 changes in pH, temperature, redox potential, or the passage of time.

The *in silico Homo sapiens* model and methods described herein can be implemented on any conventional host computer system, such as those based on Intel.RTM. 10 microprocessors and running Microsoft Windows operating systems. Other systems, such as those using the UNIX or LINUX operating system and based on IBM.RTM., DEC.RTM. or Motorola.RTM. microprocessors are also contemplated. The systems and methods described herein can also be 15 implemented to run on client-server systems and wide-area networks, such as the Internet.

Software to implement a method or model of the invention can be written in any well-known computer language, such as Java, C, C++, Visual Basic, FORTRAN 20 or COBOL and compiled using any well-known compatible compiler. The software of the invention normally runs from instructions stored in a memory on a host computer system. A memory or computer readable medium can be a hard disk, floppy disc, compact disc, magneto-optical 25 disc, Random Access Memory, Read Only Memory or Flash Memory. The memory or computer readable medium used in the invention can be contained within a single computer or distributed in a network. A network can be any of a number of conventional network systems known in the art 30 such as a local area network (LAN) or a wide area network (WAN). Client-server environments, database servers and networks that can be used in the invention are well known in the art. For example, the database server can run on an operating system such as UNIX,

running a relational database management system, a World Wide Web application and a World Wide Web server. Other types of memories and computer readable media are also contemplated to function within the scope of the 5 invention.

A database or data structure of the invention can be represented in a markup language format including, for example, Standard Generalized Markup Language (SGML), Hypertext markup language (HTML) or 10 Extensible Markup language (XML). Markup languages can be used to tag the information stored in a database or data structure of the invention, thereby providing convenient annotation and transfer of data between databases and data structures. In particular, an XML 15 format can be useful for structuring the data representation of reactions, reactants and their annotations; for exchanging database contents, for example, over a network or internet; for updating individual elements using the document object model; or 20 for providing differential access to multiple users for different information content of a data base or data structure of the invention. XML programming methods and editors for writing XML code are known in the art as described, for example, in Ray, "Learning XML" 25 O'Reilly and Associates, Sebastopol, CA (2001).

A set of constraints can be applied to a reaction network data structure to simulate the flux of mass through the reaction network under a particular set of environmental conditions specified by a 30 constraints set. Because the time constants characterizing metabolic transients and/or metabolic reactions are typically very rapid, on the order of milli-seconds to seconds, compared to the time constants of cell growth on the order of hours to days,

the transient mass balances can be simplified to only consider the steady state behavior. Referring now to an example where the reaction network data structure is a stoichiometric matrix, the steady state mass balances 5 can be applied using the following system of linear equations

$$S \cdot v = 0 \quad (\text{Eq. 5})$$

where  $S$  is the stoichiometric matrix as defined above and  $v$  is the flux vector. This equation defines the 10 mass, energy, and redox potential constraints placed on the metabolic network as a result of stoichiometry. Together Equations 1 and 5 representing the reaction constraints and mass balances, respectively, effectively define the capabilities and constraints of 15 the metabolic genotype and the organism's metabolic potential. All vectors,  $v$ , that satisfy Equation 5 are said to occur in the mathematical nullspace of  $S$ . Thus, the null space defines steady-state metabolic 20 flux distributions that do not violate the mass, energy, or redox balance constraints. Typically, the number of fluxes is greater than the number of mass balance constraints, thus a plurality of flux distributions satisfy the mass balance constraints and occupy the null space. The null space, which defines 25 the feasible set of metabolic flux distributions, is further reduced in size by applying the reaction constraints set forth in Equation 1 leading to a defined solution space. A point in this space represents a flux distribution and hence a metabolic 30 phenotype for the network. An optimal solution within the set of all solutions can be determined using mathematical optimization methods when provided with a stated objective and a constraint set. The calculation of any solution constitutes a simulation of the model.

Objectives for activity of a human cell can be chosen. While the overall objective of a multi-cellular organism may be growth or reproduction, individual human cell types generally have much more complex objectives, even to the seemingly extreme objective of apoptosis (programmed cell death), which may benefit the organism but certainly not the individual cell. For example, certain cell types may have the objective of maximizing energy production, while others have the objective of maximizing the production of a particular hormone, extracellular matrix component, or a mechanical property such as contractile force. In cases where cell reproduction is slow, such as human skeletal muscle, growth and its effects need not be taken into account. In other cases, biomass composition and growth rate could be incorporated into a "maintenance" type of flux, where rather than optimizing for growth, production of precursors is set at a level consistent with experimental knowledge and a different objective is optimized.

Certain cell types, including cancer cells, can be viewed as having an objective of maximizing cell growth. Growth can be defined in terms of biosynthetic requirements based on literature values of biomass composition or experimentally determined values such as those obtained as described above. Thus, biomass generation can be defined as an exchange reaction that removes intermediate metabolites in the appropriate ratios and represented as an objective function. In addition to draining intermediate metabolites this reaction flux can be formed to utilize energy molecules such as ATP, NADH and NADPH so as to incorporate any maintenance requirement that must be met. This new reaction flux then becomes another constraint/balance

equation that the system must satisfy as the objective function. Using the stoichiometric matrix of Figure 3 as an example, adding such a constraint is analogous to adding the additional column  $V_{growth}$  to the 5 stoichiometric matrix to represent fluxes to describe the production demands placed on the metabolic system. Setting this new flux as the objective function and asking the system to maximize the value of this flux for a given set of constraints on all the other fluxes 10 is then a method to simulate the growth of the organism.

Continuing with the example of the stoichiometric matrix applying a constraint set to a reaction network data structure can be illustrated as 15 follows. The solution to equation 5 can be formulated as an optimization problem, in which the flux distribution that minimizes a particular objective is found. Mathematically, this optimization problem can be stated as:

20 Minimize  $Z$  (Eq. 6)

where  $z = \sum c_i \cdot v_i$  (Eq. 7)

where  $Z$  is the objective which is represented as a 25 linear combination of metabolic fluxes  $v_i$  using the weights  $c_i$  in this linear combination. The optimization problem can also be stated as the equivalent maximization problem; i.e. by changing the sign on  $Z$ . Any commands for solving the optimization 30 problem can be used including, for example, linear programming commands.

A computer system of the invention can further include a user interface capable of receiving a representation of one or more reactions. A user interface of the invention can also be capable of

5 sending at least one command for modifying the data structure, the constraint set or the commands for applying the constraint set to the data representation, or a combination thereof. The interface can be a graphic user interface having graphical means for

10 making selections such as menus or dialog boxes. The interface can be arranged with layered screens accessible by making selections from a main screen. The user interface can provide access to other databases useful in the invention such as a metabolic

15 reaction database or links to other databases having information relevant to the reactions or reactants in the reaction network data structure or to *Homo sapiens* physiology. Also, the user interface can display a graphical representation of a reaction network or the

20 results of a simulation using a model of the invention.

Once an initial reaction network data structure and set of constraints has been created, this model can be tested by preliminary simulation. During preliminary simulation, gaps in the network or

25 "dead-ends" in which a metabolite can be produced but not consumed or where a metabolite can be consumed but not produced can be identified. Based on the results of preliminary simulations areas of the metabolic reconstruction that require an additional reaction can

30 be identified. The determination of these gaps can be readily calculated through appropriate queries of the reaction network data structure and need not require the use of simulation strategies, however, simulation would be an alternative approach to locating such gaps.

In the preliminary simulation testing and model content refinement stage the existing model is subjected to a series of functional tests to determine if it can perform basic requirements such as the

5 ability to produce the required biomass constituents and generate predictions concerning the basic physiological characteristics of the particular cell type being modeled. The more preliminary testing that is conducted the higher the quality of the model that

10 will be generated. Typically, the majority of the simulations used in this stage of development will be single optimizations. A single optimization can be used to calculate a single flux distribution demonstrating how metabolic resources are routed

15 determined from the solution to one optimization problem. An optimization problem can be solved using linear programming as demonstrated in the Examples below. The result can be viewed as a display of a flux distribution on a reaction map. Temporary reactions

20 can be added to the network to determine if they should be included into the model based on modeling/simulation requirements.

Once a model of the invention is sufficiently complete with respect to the content of the reaction

25 network data structure according to the criteria set forth above, the model can be used to simulate activity of one or more reactions in a reaction network. The results of a simulation can be displayed in a variety of formats including, for example, a table, graph,

30 reaction network, flux distribution map or a phenotypic phase plane graph.

Thus, the invention provides a method for predicting a *Homo sapiens* physiological function. The method includes the steps of (a) providing a data

structure relating a plurality of *Homo sapiens* reactants to a plurality of *Homo sapiens* reactions, wherein each of the *Homo sapiens* reactions includes a reactant identified as a substrate of the reaction, a 5 reactant identified as a product of the reaction and a stoichiometric coefficient relating said substrate and said product; (b) providing a constraint set for the plurality of *Homo sapiens* reactions; (c) providing an objective function, and (d) determining at least one 10 flux distribution that minimizes or maximizes the objective function when the constraint set is applied to the data structure, thereby predicting a *Homo sapiens* physiological function.

A method for predicting a *Homo sapiens* physiological function can include the steps of (a) 15 providing a data structure relating a plurality of *Homo sapiens* reactants to a plurality of *Homo sapiens* reactions, wherein each of the *Homo sapiens* reactions includes a reactant identified as a substrate of the reaction, a reactant identified as a product of the 20 reaction and a stoichiometric coefficient relating the substrate and the product, and wherein at least one of the reactions is a regulated reaction; (b) providing a constraint set for the plurality of reactions, wherein 25 the constraint set includes a variable constraint for the regulated reaction; (c) providing a condition-dependent value to the variable constraint; (d) providing an objective function, and (e) determining at least one flux distribution that 30 minimizes or maximizes the objective function when the constraint set is applied to the data structure, thereby predicting a *Homo sapiens* physiological function.

As used herein, the term "physiological function," when used in reference to *Homo sapiens*, is intended to mean an activity of a *Homo sapiens* cell as a whole. An activity included in the term can be the 5 magnitude or rate of a change from an initial state of a *Homo sapiens* cell to a final state of the *Homo sapiens* cell. An activity included in the term can be, for example, growth, energy production, redox equivalent production, biomass production, development, 10 or consumption of carbon, nitrogen, sulfur, phosphate, hydrogen or oxygen. An activity can also be an output of a particular reaction that is determined or predicted in the context of substantially all of the reactions that affect the particular reaction in a *Homo sapiens* cell or substantially all of the reactions that 15 occur in a *Homo sapiens* cell (e.g. muscle contraction). Examples of a particular reaction included in the term are production of biomass precursors, production of a protein, production of an amino acid, production of a 20 purine, production of a pyrimidine, production of a lipid, production of a fatty acid, production of a cofactor or transport of a metabolite. A physiological function can include an emergent property which emerges from the whole but not from the sum of parts where the 25 parts are observed in isolation (see for example, Palsson, Nat. Biotech 18:1147-1150 (2000)).

A physiological function of *Homo sapiens* reactions can be determined using phase plane analysis of flux distributions. Phase planes are 30 representations of the feasible set which can be presented in two or three dimensions. As an example, two parameters that describe the growth conditions such as substrate and oxygen uptake rates can be defined as two axes of a two-dimensional space. The optimal flux

distribution can be calculated from a reaction network data structure and a set of constraints as set forth above for all points in this plane by repeatedly solving the linear programming problem while adjusting 5 the exchange fluxes defining the two-dimensional space. A finite number of qualitatively different metabolic pathway utilization patterns can be identified in such a plane, and lines can be drawn to demarcate these regions. The demarcations defining the regions can be 10 determined using shadow prices of linear optimization as described, for example in Chvatal, Linear Programming New York, W.H. Freeman and Co. (1983). The regions are referred to as regions of constant shadow 15 price structure. The shadow prices define the intrinsic value of each reactant toward the objective function as a number that is either negative, zero, or positive and are graphed according to the uptake rates represented by the x and y axes. When the shadow 20 prices become zero as the value of the uptake rates are changed there is a qualitative shift in the optimal reaction network.

One demarcation line in the phenotype phase plane is defined as the line of optimality (LO). This line represents the optimal relation between respective 25 metabolic fluxes. The LO can be identified by varying the x-axis flux and calculating the optimal y-axis flux with the objective function defined as the growth flux . From the phenotype phase plane analysis the conditions under which a desired activity is optimal 30 can be determined. The maximal uptake rates lead to the definition of a finite area of the plot that is the predicted outcome of a reaction network within the environmental conditions represented by the constraint set. Similar analyses can be performed in multiple 35 dimensions where each dimension on the plot corresponds

to a different uptake rate. These and other methods for using phase plane analysis, such as those described in Edwards et al., Biotech Bioeng. 77:27-36(2002), can be used to analyze the results of a simulation using an 5 *in silico Homo sapiens* model of the invention.

A physiological function of *Homo sapiens* can also be determined using a reaction map to display a flux distribution. A reaction map of *Homo sapiens* can be used to view reaction networks at a variety of 10 levels. In the case of a cellular metabolic reaction network a reaction map can contain the entire reaction complement representing a global perspective. Alternatively, a reaction map can focus on a particular region of metabolism such as a region corresponding to 15 a reaction subsystem described above or even on an individual pathway or reaction.

Thus, the invention provides an apparatus that produces a representation of a *Homo sapiens* physiological function, wherein the representation is 20 produced by a process including the steps of: (a) providing a data structure relating a plurality of *Homo sapiens* reactants to a plurality of *Homo sapiens* reactions, wherein each of the *Homo sapiens* reactions includes a reactant identified as a substrate of the 25 reaction, a reactant identified as a product of the reaction and a stoichiometric coefficient relating said substrate and said product; (b) providing a constraint set for the plurality of *Homo sapiens* reactions; (c) providing an objective function; (d) determining at 30 least one flux distribution that minimizes or maximizes the objective function when the constraint set is applied to the data structure, thereby predicting a *Homo sapiens* physiological function, and (e) producing

a representation of the activity of the one or more *Homo sapiens* reactions.

The methods of the invention can be used to determine the activity of a plurality of *Homo sapiens* reactions including, for example, biosynthesis of an amino acid, degradation of an amino acid, biosynthesis of a purine, biosynthesis of a pyrimidine, biosynthesis of a lipid, metabolism of a fatty acid, biosynthesis of a cofactor, transport of a metabolite and metabolism of an alternative carbon source. In addition, the methods can be used to determine the activity of one or more of the reactions described above or listed in Table 1.

The methods of the invention can be used to determine a phenotype of a *Homo sapiens* mutant. The activity of one or more *Homo sapiens* reactions can be determined using the methods described above, wherein the reaction network data structure lacks one or more gene-associated reactions that occur in *Homo sapiens*. Alternatively, the methods can be used to determine the activity of one or more *Homo sapiens* reactions when a reaction that does not naturally occur in *Homo sapiens* is added to the reaction network data structure. Deletion of a gene can also be represented in a model of the invention by constraining the flux through the reaction to zero, thereby allowing the reaction to remain within the data structure. Thus, simulations can be made to predict the effects of adding or removing genes to or from *Homo sapiens*. The methods can be particularly useful for determining the effects of adding or deleting a gene that encodes for a gene product that performs a reaction in a peripheral metabolic pathway.

A drug target or target for any other agent that affects *Homo sapiens* function can be predicted using the methods of the invention. Such predictions can be made by removing a reaction to simulate total inhibition or prevention by a drug or agent.

Alternatively, partial inhibition or reduction in the activity a particular reaction can be predicted by performing the methods with altered constraints. For example, reduced activity can be introduced into a model of the invention by altering the  $a_i$  or  $b_i$  values for the metabolic flux vector of a target reaction to reflect a finite maximum or minimum flux value corresponding to the level of inhibition. Similarly, the effects of activating a reaction, by initiating or increasing the activity of the reaction, can be predicted by performing the methods with a reaction network data structure lacking a particular reaction or by altering the  $a_i$  or  $b_i$  values for the metabolic flux vector of a target reaction to reflect a maximum or minimum flux value corresponding to the level of activation. The methods can be particularly useful for identifying a target in a peripheral metabolic pathway.

Once a reaction has been identified for which activation or inhibition produces a desired effect on *Homo sapiens* function, an enzyme or macromolecule that performs the reaction in *Homo sapiens* or a gene that expresses the enzyme or macromolecule can be identified as a target for a drug or other agent. A candidate compound for a target identified by the methods of the invention can be isolated or synthesized using known methods. Such methods for isolating or synthesizing compounds can include, for example, rational design based on known properties of the target (see, for example, DeCamp et al., Protein Engineering Principles and Practice, Ed. Cleland and Craik, Wiley-Liss, New

York, pp. 467-506 (1996)), screening the target against combinatorial libraries of compounds (see for example, Houghten et al., Nature, 354, 84-86 (1991); Dooley et al., Science, 266, 2019-2022 (1994), which describe an 5 iterative approach, or R. Houghten et al. PCT/US91/08694 and U.S. Patent 5,556,762 which describe the positional-scanning approach), or a combination of both to obtain focused libraries. Those skilled in the art will know or will be able to routinely determine 10 assay conditions to be used in a screen based on properties of the target or activity assays known in the art.

A candidate drug or agent, whether identified by the methods described above or by other methods 15 known in the art, can be validated using an *in silico* *Homo sapiens* model or method of the invention. The effect of a candidate drug or agent on *Homo sapiens* physiological function can be predicted based on the activity for a target in the presence of the candidate 20 drug or agent measured *in vitro* or *in vivo*. This activity can be represented in an *in silico* *Homo sapiens* model by adding a reaction to the model, removing a reaction from the model or adjusting a constraint for a reaction in the model to reflect the 25 measured effect of the candidate drug or agent on the activity of the reaction. By running a simulation under these conditions the holistic effect of the candidate drug or agent on *Homo sapiens* physiological function can be predicted.

30 The methods of the invention can be used to determine the effects of one or more environmental components or conditions on an activity of a *Homo sapiens* cell. As set forth above an exchange reaction

can be added to a reaction network data structure corresponding to uptake of an environmental component, release of a component to the environment, or other environmental demand. The effect of the environmental 5 component or condition can be further investigated by running simulations with adjusted a<sub>j</sub> or b<sub>j</sub> values for the metabolic flux vector of the exchange reaction target reaction to reflect a finite maximum or minimum flux value corresponding to the effect of the 10 environmental component or condition. The environmental component can be, for example an alternative carbon source or a metabolite that when added to the environment of a *Homo sapiens* cell can be taken up and metabolized. The environmental component 15 can also be a combination of components present for example in a minimal medium composition. Thus, the methods can be used to determine an optimal or minimal medium composition that is capable of supporting a particular activity of *Homo sapiens*.

20 The invention further provides a method for determining a set of environmental components to achieve a desired activity for *Homo sapiens*. The method includes the steps of (a) providing a data structure relating a plurality of *Homo sapiens* 25 reactants to a plurality of *Homo sapiens* reactions, wherein each of the *Homo sapiens* reactions includes a reactant identified as a substrate of the reaction, a reactant identified as a product of the reaction and a stoichiometric coefficient relating the substrate and 30 the product; (b) providing a constraint set for the plurality of *Homo sapiens* reactions; (c) applying the constraint set to the data representation, thereby determining the activity of one or more *Homo sapiens* reactions (d) determining the activity of one or more

*Homo sapiens* reactions according to steps (a) through (c), wherein the constraint set includes an upper or lower bound on the amount of an environmental component and (e) repeating steps (a) through (c) with a changed 5 constraint set, wherein the activity determined in step (e) is improved compared to the activity determined in step (d).

The following examples are intended to illustrate but not limit the present invention.

10

EXAMPLE I

This example shows the construction of a universal *Homo sapiens* metabolic reaction database, a *Homo sapiens* core metabolic reaction database and a *Homo sapiens* muscle cell metabolic reaction database. 15 This example also shows the iterative model building process used to generate a *Homo sapiens* core metabolic model and a *Homo sapiens* muscle cell metabolic model.

A universal *Homo sapiens* reaction database was prepared from the genome databases and biochemical 20 literature. The reaction database shown in Table 1 contains the following information:

Locus ID - the locus number of the gene found in the LocusLink website.

Gene Ab. - various abbreviations which are 25 used for the gene.

Reaction Stoichiometry - includes all metabolites and direction of the reaction, as well as reversibility.

E.C. - The Enzyme Commission number.

Additional information included in the universal reaction database, although not shown in Table 1, included the chapter of Salway, supra (1999), where relevant reactions were found; the cellular 5 location, if the reaction primarily occurs in a given compartment; the SWISS PROT identifier, which can be used to locate the gene record in SWISS PROT; the full name of the gene at the given locus; the chromosomal location of the gene; the Mendelian Inheritance in Man 10 (MIM) data associated with the gene; and the tissue type, if the gene is primarily expressed in a certain tissue. Overall, 1130 metabolic enzyme- or transporter-encoding genes were included in the universal reaction database.

15       Fifty-nine reactions in the universal reaction database were identified and included based on biological data as found in Salway supra (1999), currently without genome annotation. Ten additional reactions, not described in the biochemical literature 20 or genome annotation, were subsequently included in the reaction database following preliminary simulation testing and model content refinement. These 69 reactions are shown at the end of Table 1.

From the universal *Homo sapiens* reaction 25 database shown in Table 1, a core metabolic reaction database was established, which included core metabolic reactions as well as some amino acid and fatty acid metabolic reactions, as described in Chapters 1, 3, 4, 7, 9, 10, 13, 17, 18 and 44 of J.G. Salway, Metabolism 30 at a Glance, 2<sup>nd</sup> ed., Blackwell Science, Malden, MA (1999). The core metabolic reaction database included 211 unique reactions, accounting for 737 genes in the *Homo sapiens* genome. The core metabolic reaction database was used, although not in its entirety, to

create the core metabolic model described in Example II.

To allow for the modeling of muscle cells, the core reaction database was expanded to include 446 unique reactions, accounting for 889 genes in the *Homo sapiens* genome. This skeletal muscle metabolic reaction database was used to create the skeletal muscle metabolic model described in Example II.

Once the core and muscle cell metabolic reaction databases were compiled, the reactions were represented as a metabolic network data structure, or "stoichiometric input file." For example, the core metabolic network data structure shown in Table 2 contains 33 reversible reactions, 31 non-reversible reactions, 97 matrix columns and 52 unique enzymes. Each reaction in Table 2 is represented so as to indicate the substrate or substrates (a negative number) and the product or products (a positive number); the stoichiometry; the name of each reaction (the term following the zero); and whether the reaction is reversible (an R following the reaction name). A metabolite that appears in the mitochondria is indicated by an "m," and a metabolite that appears in the extracellular space is indicated by an "ex."

To perform a preliminary simulation or to simulate a physiological condition, a set of inputs and outputs has to be defined and the network objective function specified. To calculate the maximum ATP production of the *Homo sapiens* core metabolic network using glucose as a carbon source, a non-zero uptake value for glucose was assigned and ATP production was maximized as the objective function, using the

representation shown in Table 2. The network's performance was examined by optimizing for the given objective function and the set of constraints defined in the input file, using flux balance analysis methods.

- 5 The model was refined in an iterative manner by examining the results of the simulation and implementing the appropriate changes.

Using this iterative procedure, two metabolic reaction networks were generated, representing human core metabolism and human skeletal muscle cell metabolism.

#### EXAMPLE II

This example shows how human metabolism can be accurately simulated using a *Homo sapiens* core metabolic model.

The human core metabolic reaction database shown in Table 3 was used in simulations of human core metabolism. This reaction database contains a total of 20 65 reactions, covering the classic biochemical pathways of glycolysis, the pentose phosphate pathway, the tricarboxylic acid cycle, oxidative phosphorylation, glycogen storage, the malate/aspartate shuttle, the glycerol phosphate shuttle, and plasma and 25 mitochondrial membrane transporters. The reaction network was divided into three compartments: the cytosol, mitochondria, and the extracellular space. The total number of metabolites in the network is 50, of which 35 also appear in the mitochondria. This core 30 metabolic network accounts for 250 human genes.

To perform simulations using the core metabolic network, network properties such as the P/O ratio were specified using Salway, supra (1999) as a reference. Oxidation of NADH through the Electron Transport System (ETS) was set to generate 2.5 ATP molecules (i.e. a P/O ratio of 2.5 for NADH), and that of FADH<sub>2</sub> was set to 1.5 ATP molecules (i.e. a P/O ratio of 1.5 for FADH<sub>2</sub>).

Using the core metabolic network, aerobic and anaerobic metabolisms were simulated *in silico*. Secretion of metabolic by-products was in agreement with the known physiological parameters. Maximum yield of all 12 precursor-metabolites (glucose-6-phosphate, fructose-6-phosphate, ribose-5-phosphate, erythrose-4-phosphate, triose phosphate, 3-phosphoglycerate, phosphoenolpyruvate, pyruvate, acetyl CoA,  $\alpha$ -ketoglutarate, succinyl CoA, and oxaloacetate) was examined and none found to exceed the values of its theoretical yield.

Maximum ATP yield was also examined in the cytosol and mitochondria. Salway, supra (1999) reports that in the absence of membrane proton-coupled transport systems, the energy yield is 38 ATP molecules per molecule of glucose and otherwise 31 ATP molecules per molecule of glucose. The core metabolic model demonstrated the same values as described by Salway supra (1999). Energy yield in the mitochondria was determined to be 38 molecules of ATP per glucose molecule. This is equivalent to production of energy in the absence of proton-couple transporters across mitochondrial membrane since all the protons were utilized only in oxidative phosphorylation. In the cytosol, energy yield was calculated to be 30.5 molecules of ATP per glucose molecule. This value

reflects the cost of metabolite exchange across the mitochondrial membrane as described by Salway, supra (1999).

### EXAMPLE III

5 This example shows how human muscle cell metabolism can be accurately simulated under various physiological and pathological conditions using a *Homo sapiens* muscle cell metabolic model.

As described in Example I, the core metabolic 10 model was extended to also include all the major reactions occurring in the skeletal muscle cell, adding new functions to the classical metabolic pathways found in the core model, such as fatty acid synthesis and  $\beta$ -oxidation, triacylglycerol and phospholipid 15 formation, and amino acid metabolism. Simulations were performed using the muscle cell reaction database shown in Table 4. The biochemical reactions were again compartmentalized into cytosolic and mitochondrial compartments.

20 To simulate physiological behavior of human skeletal muscle cells, an objective function had to be defined. Growth of muscle cells occurs in time scales of several hours to days. The time scale of interest in the simulation, however, was in the order of several 25 to tens of minutes, reflecting the time period of metabolic changes during exercise. Thus, contraction (defined as, and related to energy production) was chosen to be the objective function, and no additional constraints were imposed to represent growth demands in 30 the cell.

To study and test the behavior of the network, twelve physiological cases (Table 5) and five disease cases (Table 6) were examined. The input and output of metabolites were specified as indicated in Table 5, and maximum energy production and metabolite secretions were calculated and taken into account.

Table 5

Table 6

Disease	Enzyme Deficiency	Reaction Cohstrained
McArdle's disease	phosphorylase	GBE1
Tarui's disease	phosphofructokinase	PFKL
5 Phosphoglycerate kinase deficiency	phosphoglycerate kinase	PGK1R
Phosphoglycerate mutase deficiency	phosphoglycerate mutase	PGAM3R
10 Lactate dehydrogenase deficiency	Lactate dehydrogenase	LDHAR

15 The skeletal muscle model was tested for utilization of various carbon sources available during various stages of exercise and food starvation (Table 5). The by-product secretion of the network in an aerobic to anaerobic shift was qualitatively compared to physiological outcome of exercise and found to exhibit the same general features such as secretion of fermentative by-products and lowered energy yield.

20 The network behavior was also examined for five disease cases (Table 6). The test cases were chosen based on their physiological relevance to the model's predictive capabilities. In brief, McArdle's disease is marked by the impairment of glycogen breakdown. Tarui's disease is characterized by a deficiency in phosphofructokinase. The remaining diseases examined are marked by a deficiency of metabolic enzymes phosphoglycerate kinase, phosphoglycerate mutase, and lactate dehydrogenase. In 25 each case, the changes in flux and by-product secretion of metabolites were examined for an aerobic to anaerobic metabolic shift with glycogen and

phosphocreatine as the sole carbon sources to the network and pyruvate, lactate, and albumin as the only metabolic by-products allowed to leave the system. To simulate the disease cases, the corresponding deficient 5 enzyme was constrained to zero. In all cases, a severe reduction in energy production was demonstrated during exercise, representing the state of the disease as seen in clinical cases.

Throughout this application various 10 publications have been referenced. The disclosures of these publications in their entireties are hereby incorporated by reference in this application in order to more fully describe the state of the art to which this invention pertains.

15 Although the invention has been described with reference to the examples provided above, it should be understood that various modifications can be made without departing from the spirit of the invention. Accordingly, the invention is limited only 20 by the claims.

Table 1

Locus ID	Gene Ab.	Reaction Stoichiometry	E.C.
	1. Carbohydrate Metabolism		
	1.1 Glycolysis / Gluconeogenesis [PATH:hsa00010]		
<u>3098</u>	HK1	GLC + ATP $\rightarrow$ G6P + ADP	<u>2.7.1.1</u>
<u>3099</u>	HK2	GLC + ATP $\rightarrow$ G6P + ADP	<u>2.7.1.1</u>
<u>3101</u>	HK3	GLC + ATP $\rightarrow$ G6P + ADP	<u>2.7.1.1</u>
<u>2645</u>	GCK, HK4, MODY2, NIDDM	GLC + ATP $\rightarrow$ G6P + ADP	<u>2.7.1.2</u>
<u>2538</u>	G6PC, G6PT	G6P + H2O $\rightarrow$ GLC + PI	<u>3.1.3.9</u>
<u>2821</u>	GPI	G6P $\leftrightarrow$ F6P	<u>5.3.1.9</u>
<u>5211</u>	PFKL	F6P + ATP $\rightarrow$ FDP + ADP	<u>2.7.1.11</u>
<u>5213</u>	PFKM	F6P + ATP $\rightarrow$ FDP + ADP	<u>2.7.1.11</u>
<u>5214</u>	PFKP, PFK-C	F6P + ATP $\rightarrow$ FDP + ADP	<u>2.7.1.11</u>
<u>5215</u>	PFKX	F6P + ATP $\rightarrow$ FDP + ADP	<u>2.7.1.11</u>
<u>2203</u>	FBP1, FBP	FDP + H2O $\rightarrow$ F6P + PI	<u>3.1.3.11</u>
<u>8789</u>	FBP2	FDP + H2O $\rightarrow$ F6P + PI	<u>3.1.3.11</u>
<u>226</u>	ALDOA	FDP $\leftrightarrow$ T3P2 + T3P1	<u>4.1.2.13</u>
<u>229</u>	ALDOB	FDP $\leftrightarrow$ T3P2 + T3P1	<u>4.1.2.13</u>
<u>230</u>	ALDOC	FDP $\leftrightarrow$ T3P2 + T3P1	<u>4.1.2.13</u>
<u>7167</u>	TPI1	T3P2 $\leftrightarrow$ T3P1	<u>5.3.1.1</u>
<u>2597</u>	GAPD, GAPDH	T3P1 + PI + NAD $\leftrightarrow$ NADH + 13PDG	<u>1.2.1.12</u>
<u>26330</u>	GAPDS, GAPDH-2	T3P1 + PI + NAD $\leftrightarrow$ NADH + 13PDG	<u>1.2.1.12</u>
<u>5230</u>	PGK1, PGKA	13PDG + ADP $\leftrightarrow$ 3PG + ATP	<u>2.7.2.3</u>
<u>5233</u>	PGK2	13PDG + ADP $\leftrightarrow$ 3PG + ATP	<u>2.7.2.3</u>
<u>5223</u>	PGAM1, PGAMA	13PDG $\rightarrow$ 23PDG	<u>5.4.2.4</u>
		23PDG + H2O $\rightarrow$ 3PG + PI	<u>3.1.3.13</u>
<u>5224</u>	PGAM2, PGAMM	3PG $\leftrightarrow$ 2PG	<u>5.4.2.1</u>
		13PDG $\leftrightarrow$ 23PDG	<u>5.4.2.4</u>
		23PDG + H2O $\rightarrow$ 3PG + PI	<u>3.1.3.13</u>
		3PG $\leftrightarrow$ 2PG	<u>5.4.2.1</u>
<u>669</u>	BPGM	13PDG $\leftrightarrow$ 23PDG	<u>5.4.2.4</u>
		23PDG + H2O $\leftrightarrow$ 3PG + PI	<u>3.1.3.13</u>
		3PG $\leftrightarrow$ 2PG	<u>5.4.2.1</u>
<u>2023</u>	ENO1, PPH, ENO1L1	2PG $\leftrightarrow$ PEP + H2O	<u>4.2.1.11</u>
<u>2026</u>	ENO2	2PG $\leftrightarrow$ PEP + H2O	<u>4.2.1.11</u>
<u>2027</u>	ENO3	2PG $\leftrightarrow$ PEP + H2O	<u>4.2.1.11</u>
<u>26237</u>	ENO1B	2PG $\leftrightarrow$ PEP + H2O	<u>4.2.1.11</u>
<u>5313</u>	PKLR, PK1	PEP + ADP $\rightarrow$ PYR + ATP	<u>2.7.1.40</u>
<u>5315</u>	PKM2, PK3, THBP1, OIP3	PEP + ADP $\rightarrow$ PYR + ATP	<u>2.7.1.40</u>
<u>5160</u>	PDHA1, PHE1A, PDHA	PYRm + COAm + NADm $\rightarrow$ NADHm + CO2m + ACCOAm	<u>1.2.4.1</u>
<u>5161</u>	PDHA2, PDHAL	PYRm + COAm + NADm $\rightarrow$ NADHm + CO2m + ACCOAm	<u>1.2.4.1</u>
<u>5162</u>	PDHB	PYRm + COAm + NADm $\rightarrow$ NADHm + CO2m + ACCOAm	<u>1.2.4.1</u>
<u>1737</u>	DLAT, DLTA, PDC-E2	PYRm + COAm + NADm $\rightarrow$ NADHm + CO2m + ACCOAm	<u>2.3.1.12</u>
<u>8050</u>	PDX1, E3BP	PYRm + COAm + NADm $\rightarrow$ NADHm + CO2m + ACCOAm	<u>2.3.1.12</u>
<u>3939</u>	LDHA, LDH1	NAD + LAC $\leftrightarrow$ PYR + NADH	<u>1.1.1.27</u>
<u>3945</u>	LDHB	NAD + LAC $\leftrightarrow$ PYR + NADH	<u>1.1.1.27</u>
<u>3948</u>	LDHC, LDH3	NAD + LAC $\leftrightarrow$ PYR + NADH	<u>1.1.1.27</u>
<u>5236</u>	PGM1	G1P $\leftrightarrow$ G6P	<u>5.4.2.2</u>
<u>5237</u>	PGM2	G1P $\leftrightarrow$ G6P	<u>5.4.2.2</u>
<u>5238</u>	PGM3	G1P $\leftrightarrow$ G6P	<u>5.4.2.2</u>
<u>1738</u>	DLD, LAD, PHE3, DLDH, E3	DLIPOm + FADm $\leftrightarrow$ LIPOm + FADH2m	<u>1.8.1.4</u>
<u>124</u>	ADH1	ETH + NAD $\leftrightarrow$ ACAL + NADH	<u>1.1.1.1</u>
<u>125</u>	ADH2	ETH + NAD $\leftrightarrow$ ACAL + NADH	<u>1.1.1.1</u>
<u>126</u>	ADH3	ETH + NAD $\leftrightarrow$ ACAL + NADH	<u>1.1.1.1</u>
<u>127</u>	ADH4	ETH + NAD $\leftrightarrow$ ACAL + NADH	<u>1.1.1.1</u>
<u>128</u>	ADH5	FALD + RGT + NAD $\leftrightarrow$ FGT + NADH	<u>1.2.1.1</u>
<u>130</u>	ADH6	ETH + NAD $\leftrightarrow$ ACAL + NADH	<u>1.1.1.1</u>
<u>131</u>	ADH7	ETH + NAD $\leftrightarrow$ ACAL + NADH	<u>1.1.1.1</u>
<u>10327</u>	AKR1A1, ALR, ALDR1	ETH + NAD $\leftrightarrow$ ACAL + NADH	<u>1.1.1.2</u>
<u>97</u>	ACYP1	ETH + NAD $\leftrightarrow$ ACAL + NADH	<u>3.6.1.7</u>
<u>98</u>	ACYP2	ETH + NAD $\leftrightarrow$ ACAL + NADH	<u>3.6.1.7</u>
	1.2 Citrate cycle (TCA cycle) PATH:hsa00020		
<u>1431</u>	CS	ACCOAm + OAm + H2O <sub>m</sub> $\rightarrow$ COAm + CIT <sub>m</sub>	<u>4.1.3.7</u>
<u>48</u>	ACO1, IREB1, IRP1	CIT $\leftrightarrow$ CIT	<u>4.2.1.3</u>
<u>50</u>	ACO2	CIT <sub>m</sub> $\leftrightarrow$ CIT	<u>4.2.1.3</u>
<u>3417</u>	IDH1	CIT + NADP $\rightarrow$ NADPH + CO <sub>2</sub> + AKG	<u>1.1.1.42</u>

<u>3418</u> IDH2	ICITm + NADPm $\rightarrow$ NADPHm + CO2m + AKGm	<u>1.1.1.42</u>
<u>3419</u> IDH3A	ICITm + NADm $\rightarrow$ CO2m + NADHm + AKGm	<u>1.1.1.41</u>
<u>3420</u> IDH3B	ICITm + NADm $\rightarrow$ CO2m + NADHm + AKGm	<u>1.1.1.41</u>
<u>3421</u> IDH3G	ICITm + NADm $\rightarrow$ CO2m + NADHm + AKGm	<u>1.1.1.41</u>
<u>4967</u> OGDH	AKGm + NADm + COAm $\rightarrow$ CO2m + NADHm + SUCCOAm	<u>1.2.4.2</u>
<u>1743</u> DLST, DLTS	AKGm + NADm + COAm $\rightarrow$ CO2m + NADHm + SUCCOAm	<u>2.3.1.61</u>
<u>8802</u> SUCLG1, SUCLA1	GTPm + SUCCm + COAm $\leftrightarrow$ GDPm + Plm + SUCCOAm	<u>6.2.1.4</u>
<u>8803</u> SUCLA2	ATPm + SUCCm + COAm $\leftrightarrow$ ADPm + Plm + SUCCOAm	<u>6.2.1.4</u>
<u>2271</u> FH	FUMm + H2O $\leftrightarrow$ MALm	<u>4.2.1.2</u>
<u>4190</u> MDH1	MAL + NAD $\leftrightarrow$ NADH + OA	<u>1.1.1.37</u>
<u>4191</u> MDH2	MALm + NADm $\leftrightarrow$ NADHm + OAm	<u>1.1.1.37</u>
<u>5091</u> PC, PCB	PYRm + ATPm + CO2m $\rightarrow$ ADPm + OAm + Plm	<u>6.4.1.1</u>
47 ACLY, ATPCL, CLATP	ATP + CIT + COA + H2O $\rightarrow$ ADP + PI + ACCOA + OA	<u>4.1.3.8</u>
<u>3657</u>	OA + GTP $\rightarrow$ PEP + GDP + CO2	<u>4.1.1.32</u>
<u>5105</u> PCK1	OAm + GTPm $\rightarrow$ PEPm + GDPm + CO2m	<u>4.1.1.32</u>
<u>5106</u> PCK2, PEPCK		
1.3 Pentose phosphate cycle PATH:hsa00030		
<u>2539</u> G6PD, G6PD1	G6P + NADP $\leftrightarrow$ D6PGL + NADPH	<u>1.1.1.49</u>
<u>9563</u> H6PD	D6PGL + H2O $\rightarrow$ D6PGC	<u>1.1.1.47</u>
	D6PGL + H2O $\rightarrow$ D6PGC	<u>3.1.1.31</u>
<u>25796</u> PGLS, 6PGL	D6PGC + NADP $\rightarrow$ NADPH + CO2 + RL5P	<u>3.1.1.31</u>
<u>5226</u> PGD	RL5P $\leftrightarrow$ X5P	<u>1.1.1.44</u>
<u>6120</u> RPE	R5P + X5P $\leftrightarrow$ T3P1 + S7P	<u>5.1.3.1</u>
<u>7086</u> TKT	X5P + E4P $\leftrightarrow$ F6P + T3P1	<u>2.2.1.1</u>
	R5P + X5P $\leftrightarrow$ T3P1 + S7P	
<u>8277</u> TKTL1, TKR, TKT2	X5P + E4P $\leftrightarrow$ F6P + T3P1	<u>2.2.1.1</u>
	T3P1 + S7P $\leftrightarrow$ E4P + F6P	
<u>6888</u> TALDO1	R5P + ATP $\leftrightarrow$ PRPP + AMP	<u>2.7.6.1</u>
<u>5631</u> PRPS1, PRS I, PRS, I	R5P + ATP $\leftrightarrow$ PRPP + AMP	<u>2.7.6.1</u>
<u>5634</u> PRPS2, PRS II, PRS, II	R5P + ATP $\leftrightarrow$ PRPP + AMP	<u>1.1.1.47</u>
<u>2663</u> GDH		
1.4 Pentose and glucuronate interconversions PATH:hsa00040		
<u>231</u> AKR1B1, AR, ALDR1, ADR	G1P + UTP $\rightarrow$ UDPG + PPI	<u>1.1.1.21</u>
<u>7359</u> UGP1	G1P + UTP $\rightarrow$ UDPG + PPI	<u>2.7.7.9</u>
<u>7360</u> UGP2, UGPP2		<u>2.7.7.9</u>
<u>7358</u> UGDPH, UDPGDH		<u>1.1.1.22</u>
<u>10720</u> UGT2B11		<u>2.4.1.17</u>
<u>54658</u> UGT1A1, UGT1A, GNT1, UGT1		<u>2.4.1.17</u>
<u>7361</u> UGT1A, UGT1, UGT1A		<u>2.4.1.17</u>
<u>7362</u> UGT2B, UGT2, UGT2B		<u>2.4.1.17</u>
<u>7363</u> UGT2B4, UGT2B11		<u>2.4.1.17</u>
<u>7364</u> UGT2B7, UGT2B9		<u>2.4.1.17</u>
<u>7365</u> UGT2B10		<u>2.4.1.17</u>
<u>7366</u> UGT2B15, UGT2B8		<u>2.4.1.17</u>
<u>7367</u> UGT2B17		<u>3.1.1.-</u>
13 AADAC, DAC		<u>3.1.1.-</u>
<u>3991</u> LIPE, LHS, HSL		<u>3.1.1.-</u>
1.5 Fructose and mannose metabolism PATH:hsa00051		
<u>4351</u> MPI, PMI1	MAN6P $\leftrightarrow$ F6P	<u>5.3.1.8</u>
<u>5372</u> PMM1	MAN6P $\leftrightarrow$ MAN1P	<u>5.4.2.8</u>
<u>5373</u> PMM2, CDG1, CDGS	MAN6P $\leftrightarrow$ MAN1P	<u>5.4.2.8</u>
<u>2762</u> GMDS		<u>4.2.1.47</u>
<u>8790</u> FPGT, GFPP	ATP + F6P $\rightarrow$ ADP + F26P	<u>2.7.1.105</u>
<u>5207</u> PFKFB1, PFRX	F26P $\rightarrow$ F6P + PI	<u>3.1.3.46</u>
	ATP + F6P $\rightarrow$ ADP + F26P	<u>2.7.1.105</u>
<u>5208</u> PFKFB2	F26P $\rightarrow$ F6P + PI	<u>3.1.3.46</u>
	ATP + F6P $\rightarrow$ ADP + F26P	<u>2.7.1.105</u>
<u>5209</u> PFKFB3	F26P $\rightarrow$ F6P + PI	<u>3.1.3.46</u>
	ATP + F6P $\rightarrow$ ADP + F26P	<u>2.7.1.105</u>
<u>5210</u> PFKFB4	F26P $\rightarrow$ F6P + PI	<u>3.1.3.46</u>
	ATP + F6P $\rightarrow$ ADP + F26P	<u>2.7.1.105</u>
	F26P $\rightarrow$ F6P + PI	<u>3.1.3.46</u>
<u>3795</u> KHK	DSOT + NAD $\rightarrow$ FRU + NADH	<u>3.1.3.46</u>
<u>6652</u> SORD		<u>2.7.1.3</u>
<u>2526</u> FUT4, FCT3A, FUC-TIV		<u>1.1.1.14</u>
<u>2529</u> FUT7		<u>2.4.1.-</u>
<u>3036</u> HAS1, HAS		<u>2.4.1.-</u>
<u>3037</u> HAS2		<u>2.4.1.-</u>

8473 OGT, O-GLCNAC	2.4.1.c
51144 LOC51144	1.1.1.c
1.6 Galactose metabolism PATH:hsa00052	
2584 GALK1, GALK	2.7.1.6
2585 GALK2, GK2	2.7.1.6
2592 GALT	2.7.7.10
2582 GALE	5.1.3.2
2720 GLB1	3.2.1.23
3938 LCT, LAC	3.2.1.62
	3.2.1.108
2683 B4GALT1, GGTB2, BETA4GAL-T1, GT1, GTB	2.4.1.90
	2.4.1.38
	2.4.1.22
3906 LALBA	2.4.1.22
2717 GLA, GALA	3.2.1.22
2548 GAA	3.2.1.20
2594 GANAB	3.2.1.20
2595 GANC	3.2.1.20
8972 MGAM, MG, MGA	3.2.1.20
	3.2.1.3
1.7 Ascorbate and aldarate metabolism PATH:hsa00053	
216 ALDH1, PUMB1	1.2.1.3
217 ALDH2	1.2.1.3
219 ALDH5, ALDHX	1.2.1.3
223 ALDH9, E3	1.2.1.3
	1.2.1.19
224 ALDH10, FALDH, SLS	1.2.1.3
8854 RALDH2	1.2.1.3
1591 CYP24	1.14.22
1592 CYP26A1, P450RA1	1.14.22
1593 CYP27A1, CXT, CYP27	1.14.22
1594 CYP27B1, PDDR, VDDR1, VDR, CYP1, VDDR, I, P450C1	1.14.22
1.8 Pyruvate metabolism PATH:hsa00620	
54988 FLJ20581	6.2.1.1
31 ACACA, ACAC, ACC	6.4.1.2
	6.3.4.14
32 ACACB, ACCB, HACC275, ACC2	6.4.1.2
	6.3.4.14
2739 GLO1, GLY1	4.4.1.5
3029 HAGH, GLO2	3.1.2.6
2223 FDH	1.2.1.1
9380 GRHPR, GLXR	1.1.1.79
4200 ME2	1.1.1.38
10873 ME3	1.1.1.40
29897 HUMNDME	1.1.1.40
4199 ME1	1.1.1.40
38 ACAT1, ACAT, T2, THIL, MAT	2.3.1.9
39 ACAT2	2.3.1.9
1.9 Glyoxylate and dicarboxylate metabolism PATH:hsa00630	
5240 PGP	3.1.3.18
2758 GLYD	1.1.1.29
10797 MTHFD2, NMDMC	3.5.4.9
	1.5.1.15
4522 MTHFD1	1.5.1.15
	3.5.4.9
	6.3.4.3
1.10 Propanoate metabolism PATH:hsa00640	
34 ACADM, MCAD	1.3.99.3
35 ACADSB	1.3.99.3

	IBCOAm + FADm $\rightarrow$ MACOAm + FADH2m	
	IVCOAm + FADm $\rightarrow$ MRCOAm + FADH2m	<u>4.2.1.17</u>
<u>1892</u> ECHS1, SCEH	MACOAm + H2O <sub>m</sub> $\rightarrow$ HIBCOAm	
	MCCOAm + H2O <sub>m</sub> $\rightarrow$ MHVCOAm	<u>1.1.1.35</u>
<u>1962</u> EHHADH	MHVCOAm + NADm $\rightarrow$ MAACOAm + NADHm	
	HIBm + NADm $\rightarrow$ MMAm + NADHm	<u>4.2.1.17</u>
	MACOAm + H2O <sub>m</sub> $\rightarrow$ HIBCOAm	
	MCCOAm + H2O <sub>m</sub> $\rightarrow$ MHVCOAm	<u>4.2.1.17</u>
<u>3030</u> HADHA, MTPA, GBP	MHVCOAm + NADm $\rightarrow$ MAACOAm + NADHm	<u>1.1.1.35</u>
	HIBm + NADm $\rightarrow$ MMAm + NADHm	
	MACOAm + H2O <sub>m</sub> $\rightarrow$ HIBCOAm	<u>4.2.1.17</u>
	MCCOAm + H2O <sub>m</sub> $\rightarrow$ MHVCOAm	
	C160CARm + COAm + FADm + NADm $\rightarrow$ FADH2m + NADHm +	<u>1.1.1.35</u>
	C140COAm + ACCOAm	<u>4.2.1.17</u>
		<u>4.1.1.9</u>
<u>23417</u> MLYCD, MCD	GABA + AKG $\rightarrow$ SUCCSAL + GLU	<u>2.6.1.19</u>
<u>18</u> ABAT, GABAT	PROPCOAm + CO2m + ATPm $\rightarrow$ ADPm + Pi <sub>m</sub> + DMMCOAm	<u>6.4.1.3</u>
<u>5095</u> PCCA	PROPCOAm + CO2m + ATPm $\rightarrow$ ADPm + Pi <sub>m</sub> + DMMCOAm	<u>6.4.1.3</u>
<u>5096</u> PCCB	LMMCOAm $\rightarrow$ SUCCOAm	<u>5.4.99.2</u>
<u>4594</u> MUT, MCM	MMAm + COAm + NADm $\rightarrow$ NADHm + CO2m + PROPCOAm	<u>1.2.1.27</u>
<u>4329</u> MMSDH		<u>6.2.1-</u>
<u>8523</u> FACVL1, VLCS, VLACS		
1.11 Butanoate metabolism PATH:hsa00650	C140COAm + 7 COAm + 7 FADm + 7 NADm $\rightarrow$ 7 FADH2m + 7 NADHm + 7 ACCOAm	<u>1.1.1.35</u>
		<u>1.1.1.35</u>
<u>3028</u> HADH2, ERAB	MBCOAm + FADm $\rightarrow$ MCCOAm + FADH2m	<u>1.3.99.2</u>
<u>3033</u> HADHSC, SCHAD	IBCOAm + FADm $\rightarrow$ MACOAm + FADH2m	
<u>35</u> ACADS, SCAD		<u>1.2.1.24</u>
<u>7915</u> ALDH5A1, SSADH, SSDH	GLU $\rightarrow$ GABA + CO <sub>2</sub>	<u>4.1.1.15</u>
<u>2571</u> GAD1, GAD, GAD67, GAD25	GLU $\rightarrow$ GABA + CO <sub>2</sub>	<u>4.1.1.15</u>
<u>2572</u> GAD2	GLU $\rightarrow$ GABA + CO <sub>2</sub>	<u>4.1.1.15</u>
<u>2573</u> GAD3	H3MCOA + COA $\leftrightarrow$ ACCOA + AACCOA	<u>4.1.3.5</u>
<u>3157</u> HMGCS1, HMGCS	H3MCOA + COA $\leftrightarrow$ ACCOA + AACCOA	<u>4.1.3.5</u>
<u>3158</u> HMGCS2	H3MCOAm $\rightarrow$ ACCOAm + ACTACm	<u>4.1.3.4</u>
<u>3155</u> HMGCL, HL		<u>2.8.3.5</u>
<u>5019</u> OXCT	3HBm + NADm $\rightarrow$ NADHm + Hm + ACTACm	<u>1.1.1.30</u>
<u>622</u> BDH	OMVALm + COAm + NADm $\rightarrow$ MBCOAm + NADHm + CO2m	<u>2.3.1-</u>
<u>1629</u> DBT, BCATE2	OIVALm + COAm + NADm $\rightarrow$ IBCOAm + NADHm + CO2m	
	OICAPm + COAm + NADHm $\rightarrow$ IVCOAm + NADHm + CO2m	
1.13 Inositol metabolism PATH:hsa00031		
2. Energy Metabolism		
2.1 Oxidative phosphorylation PATH:hsa00190		
<u>4535</u> MTND1	NADHm + Qm + 4 Hm $\rightarrow$ QH2m + NADm + 4 H	<u>1.6.5.3</u>
<u>4536</u> MTND2	NADHm + Qm + 4 Hm $\rightarrow$ QH2m + NADm + 4 H	<u>1.6.5.3</u>
<u>4537</u> MTND3	NADHm + Qm + 4 Hm $\rightarrow$ QH2m + NADm + 4 H	<u>1.6.5.3</u>
<u>4538</u> MTND4	NADHm + Qm + 4 Hm $\rightarrow$ QH2m + NADm + 4 H	<u>1.6.5.3</u>
<u>4539</u> MTND4L	NADHm + Qm + 4 Hm $\rightarrow$ QH2m + NADm + 4 H	<u>1.6.5.3</u>
<u>4540</u> MTND5	NADHm + Qm + 4 Hm $\rightarrow$ QH2m + NADm + 4 H	<u>1.6.5.3</u>
<u>4541</u> MTND6	NADHm + Qm + 4 Hm $\rightarrow$ QH2m + NADm + 4 H	<u>1.6.5.3</u>
<u>4694</u> NDUFA1, MWFE	NADHm + Qm + 4 Hm $\rightarrow$ QH2m + NADm + 4 H	<u>1.6.5.3</u>
<u>4695</u> NDUFA2, B8	NADHm + Qm + 4 Hm $\rightarrow$ QH2m + NADm + 4 H	<u>1.6.99.3</u>
<u>4696</u> NDUFA3, B9	NADHm + Qm + 4 Hm $\rightarrow$ QH2m + NADm + 4 H	<u>1.6.5.3</u>
<u>4697</u> NDUFA4, MLRQ	NADHm + Qm + 4 Hm $\rightarrow$ QH2m + NADm + 4 H	<u>1.6.99.3</u>
<u>4698</u> NDUFA5, UQOR13, B13	NADHm + Qm + 4 Hm $\rightarrow$ QH2m + NADm + 4 H	<u>1.6.5.3</u>
<u>4700</u> NDUFA6, B14	NADHm + Qm + 4 Hm $\rightarrow$ QH2m + NADm + 4 H	<u>1.6.99.3</u>
<u>4701</u> NDUFA7, B14.5a, B14.5A	NADHm + Qm + 4 Hm $\rightarrow$ QH2m + NADm + 4 H	<u>1.6.5.3</u>
<u>4702</u> NDUFA8, PGIV	NADHm + Qm + 4 Hm $\rightarrow$ QH2m + NADm + 4 H	<u>1.6.99.3</u>
<u>4704</u> NDUFA9, NDUFS2L	NADHm + Qm + 4 Hm $\rightarrow$ QH2m + NADm + 4 H	<u>1.6.5.3</u>
<u>4705</u> NDUFA10	NADHm + Qm + 4 Hm $\rightarrow$ QH2m + NADm + 4 H	<u>1.6.99.3</u>
		<u>1.6.5.3</u>

<u>4706</u> NDUFAB1, SDAP	NADHm + Qm + 4 Hm $\rightarrow$ QH2m + NADm + 4 H	<u>1.6.99.3</u>
<u>4707</u> NDUFB1, MNLL, CI-SGDH	NADHm + Qm + 4 Hm $\rightarrow$ QH2m + NADm + 4 H	<u>1.6.5.3</u>
<u>4708</u> NDUFB2, AGGG	NADHm + Qm + 4 Hm $\rightarrow$ QH2m + NADm + 4 H	<u>1.6.99.3</u>
<u>4709</u> NDUFB3, B12	NADHm + Qm + 4 Hm $\rightarrow$ QH2m + NADm + 4 H	<u>1.6.5.3</u>
<u>4710</u> NDUFB4, B15	NADHm + Qm + 4 Hm $\rightarrow$ QH2m + NADm + 4 H	<u>1.6.99.3</u>
<u>4711</u> NDUFB5, SGDH	NADHm + Qm + 4 Hm $\rightarrow$ QH2m + NADm + 4 H	<u>1.6.5.3</u>
<u>4712</u> NDUFB6, B17	NADHm + Qm + 4 Hm $\rightarrow$ QH2m + NADm + 4 H	<u>1.6.99.3</u>
<u>4713</u> NDUFB7, B18	NADHm + Qm + 4 Hm $\rightarrow$ QH2m + NADm + 4 H	<u>1.6.5.3</u>
<u>4714</u> NDUFB8, ASHI	NADHm + Qm + 4 Hm $\rightarrow$ QH2m + NADm + 4 H	<u>1.6.99.3</u>
<u>4715</u> NDUFB9, UQOR22, B22	NADHm + Qm + 4 Hm $\rightarrow$ QH2m + NADm + 4 H	<u>1.6.5.3</u>
<u>4716</u> NDUFB10, PDSW	NADHm + Qm + 4 Hm $\rightarrow$ QH2m + NADm + 4 H	<u>1.6.99.3</u>
<u>4717</u> NDUFC1, KFY1	NADHm + Qm + 4 Hm $\rightarrow$ QH2m + NADm + 4 H	<u>1.6.5.3</u>
<u>4718</u> NDUFC2, B14.5b, B14.5B	NADHm + Qm + 4 Hm $\rightarrow$ QH2m + NADm + 4 H	<u>1.6.5.3</u>
<u>4724</u> NDUFS4, AQDQ	NADHm + Qm + 4 Hm $\rightarrow$ QH2m + NADm + 4 H	<u>1.6.99.3</u>
<u>4725</u> NDUFS5	NADHm + Qm + 4 Hm $\rightarrow$ QH2m + NADm + 4 H	<u>1.6.5.3</u>
<u>4726</u> NDUFS6	NADHm + Qm + 4 Hm $\rightarrow$ QH2m + NADm + 4 H	<u>1.6.99.3</u>
<u>4731</u> NDUFV3	NADHm + Qm + 4 Hm $\rightarrow$ QH2m + NADm + 4 H	<u>1.6.5.3</u>
<u>4727</u> NDUFS7, PSST	NADHm + Qm + 4 Hm $\rightarrow$ QH2m + NADm + 4 H	<u>1.6.99.3</u>
<u>4722</u> NDUFS3	NADHm + Qm + 4 Hm $\rightarrow$ QH2m + NADm + 4 H	<u>1.6.5.3</u>
<u>4720</u> NDUFS2	NADHm + Qm + 4 Hm $\rightarrow$ QH2m + NADm + 4 H	<u>1.6.99.3</u>
<u>4729</u> NDUFV2	NADHm + Qm + 4 Hm $\rightarrow$ QH2m + NADm + 4 H	<u>1.6.5.3</u>
<u>4723</u> NDUFV1, UQOR1	NADHm + Qm + 4 Hm $\rightarrow$ QH2m + NADm + 4 H	<u>1.6.99.3</u>
<u>4719</u> NDUFS1, PRO1304	NADHm + Qm + 4 Hm $\rightarrow$ QH2m + NADm + 4 H	<u>1.6.99.3</u>
<u>4728</u> NDUFS8	NADHm + Qm + 4 Hm $\rightarrow$ QH2m + NADm + 4 H	<u>1.6.5.3</u>
<u>6391</u> SDHC	SUCCm + FADm $\leftrightarrow$ FUMm + FADH2m FADH2m + Qm $\leftrightarrow$ FADm + QH2m	<u>1.3.5.1</u>
<u>6392</u> SDHD, CBT1, PGL, PGL1	SUCCm + FADm $\leftrightarrow$ FUMm + FADH2m FADH2m + Qm $\leftrightarrow$ FADm + QH2m	<u>1.3.5.1</u>
<u>6389</u> SDHA, SDH2, SDHF, FP	SUCCm + FADm $\leftrightarrow$ FUMm + FADH2m FADH2m + Qm $\leftrightarrow$ FADm + QH2m	<u>1.3.5.1</u>
<u>6390</u> SDHB, SDH1, IP, SDH	SUCCm + FADm $\leftrightarrow$ FUMm + FADH2m FADH2m + Qm $\leftrightarrow$ FADm + QH2m	<u>1.3.5.1</u>
<u>7386</u> UQCRCFS1, RIS1	O2m + 4 FEROm + 4 Hm $\rightarrow$ 4 FERIm + 2 H2Om + 4 H	<u>1.10.2.2</u>
<u>4519</u> MTCYB	O2m + 4 FEROm + 4 Hm $\rightarrow$ 4 FERIm + 2 H2Om + 4 H	<u>1.10.2.2</u>
<u>1537</u> CYC1	O2m + 4 FEROm + 4 Hm $\rightarrow$ 4 FERIm + 2 H2Om + 4 H	<u>1.10.2.2</u>
<u>7384</u> UQCRC1, D3S3191	O2m + 4 FEROm + 4 Hm $\rightarrow$ 4 FERIm + 2 H2Om + 4 H	<u>1.10.2.2</u>
<u>7385</u> UQCRC2	O2m + 4 FEROm + 4 Hm $\rightarrow$ 4 FERIm + 2 H2Om + 4 H	<u>1.10.2.2</u>
<u>7388</u> UQCRC	O2m + 4 FEROm + 4 Hm $\rightarrow$ 4 FERIm + 2 H2Om + 4 H	<u>1.10.2.2</u>
<u>7381</u> UQCRCB, QPC, UQBPF, QP-C	O2m + 4 FEROm + 4 Hm $\rightarrow$ 4 FERIm + 2 H2Om + 4 H	<u>1.10.2.2</u>
<u>27089</u> QP-C	O2m + 4 FEROm + 4 Hm $\rightarrow$ 4 FERIm + 2 H2Om + 4 H	<u>1.10.2.2</u>
<u>10975</u> UQCRC	O2m + 4 FEROm + 4 Hm $\rightarrow$ 4 FERIm + 2 H2Om + 4 H	<u>1.10.2.2</u>
<u>1333</u> COX5BL4	QH2m + 2 FERIm + 4 Hm $\rightarrow$ Qm + 2 FEROm + 4 H	<u>1.9.3.1</u>
<u>4514</u> MTCO3	QH2m + 2 FERIm + 4 Hm $\rightarrow$ Qm + 2 FEROm + 4 H	<u>1.9.3.1</u>
<u>4512</u> MTCO1	QH2m + 2 FERIm + 4 Hm $\rightarrow$ Qm + 2 FEROm + 4 H	<u>1.9.3.1</u>

<u>4513</u> MTCO2	QH2m + 2 FERIm + 4 Hm $\rightarrow$ Qm + 2 FEROm + 4 H	<u>1.9.3.1</u>
<u>1329</u> COX5B	QH2m + 2 FERIm + 4 Hm $\rightarrow$ Qm + 2 FEROm + 4 H	<u>1.9.3.1</u>
<u>1327</u> COX4	QH2m + 2 FERIm + 4 Hm $\rightarrow$ Qm + 2 FEROm + 4 H	<u>1.9.3.1</u>
<u>1337</u> COX6A1, COX6A	QH2m + 2 FERIm + 4 Hm $\rightarrow$ Qm + 2 FEROm + 4 H	<u>1.9.3.1</u>
<u>1339</u> COX6A2	QH2m + 2 FERIm + 4 Hm $\rightarrow$ Qm + 2 FEROm + 4 H	<u>1.9.3.1</u>
<u>1340</u> COX6B	QH2m + 2 FERIm + 4 Hm $\rightarrow$ Qm + 2 FEROm + 4 H	<u>1.9.3.1</u>
<u>1345</u> COX6C	QH2m + 2 FERIm + 4 Hm $\rightarrow$ Qm + 2 FEROm + 4 H	<u>1.9.3.1</u>
<u>9377</u> COX5A, COX, VA, COX-VA	QH2m + 2 FERIm + 4 Hm $\rightarrow$ Qm + 2 FEROm + 4 H	<u>1.9.3.1</u>
<u>1346</u> COX7A1, COX7AM, COX7A	QH2m + 2 FERIm + 4 Hm $\rightarrow$ Qm + 2 FEROm + 4 H	<u>1.9.3.1</u>
<u>1347</u> COX7A2, COX VIIa-L	QH2m + 2 FERIm + 4 Hm $\rightarrow$ Qm + 2 FEROm + 4 H	<u>1.9.3.1</u>
<u>1348</u> COX7A3	QH2m + 2 FERIm + 4 Hm $\rightarrow$ Qm + 2 FEROm + 4 H	<u>1.9.3.1</u>
<u>1349</u> COX7B	QH2m + 2 FERIm + 4 Hm $\rightarrow$ Qm + 2 FEROm + 4 H	<u>1.9.3.1</u>
<u>9167</u> COX7A2L, COX7RP, EB1	QH2m + 2 FERIm + 4 Hm $\rightarrow$ Qm + 2 FEROm + 4 H	<u>1.9.3.1</u>
<u>1350</u> COX7C	QH2m + 2 FERIm + 4 Hm $\rightarrow$ Qm + 2 FEROm + 4 H	<u>1.9.3.1</u>
<u>1351</u> COX8, COX VIII	QH2m + 2 FERIm + 4 Hm $\rightarrow$ Qm + 2 FEROm + 4 H	<u>1.9.3.1</u>
<u>4508</u> MTATP6	ADPm + Pim + 3 H $\rightarrow$ ATPm + 3 Hm + H2Om	<u>3.6.1.34</u>
<u>4509</u> MTATP8	ADPm + Pim + 3 H $\rightarrow$ ATPm + 3 Hm + H2Om	<u>3.6.1.34</u>
<u>499</u> ATP5A2	ADPm + Pim + 3 H $\rightarrow$ ATPm + 3 Hm + H2Om	<u>3.6.1.34</u>
<u>507</u> ATP5B1, ATPSBL1	ADPm + Pim + 3 H $\rightarrow$ ATPm + 3 Hm + H2Om	<u>3.6.1.34</u>
<u>508</u> ATP5B2, ATPSBL2	ADPm + Pim + 3 H $\rightarrow$ ATPm + 3 Hm + H2Om	<u>3.6.1.34</u>
<u>519</u> ATP5H	ADPm + Pim + 3 H $\rightarrow$ ATPm + 3 Hm + H2Om	<u>3.6.1.34</u>
<u>537</u> ATP6S1, ORF, VATPS1, XAP-3	ADPm + Pim + 3 H $\rightarrow$ ATPm + 3 Hm + H2Om	<u>3.6.1.34</u>
<u>514</u> ATP5E	ADPm + Pim + 3 H $\rightarrow$ ATPm + 3 Hm + H2Om	<u>3.6.1.34</u>
<u>513</u> ATP5D	ADPm + Pim + 3 H $\rightarrow$ ATPm + 3 Hm + H2Om	<u>3.6.1.34</u>
<u>506</u> ATP5B, ATPSB	ADPm + Pim + 3 H $\rightarrow$ ATPm + 3 Hm + H2Om	<u>3.6.1.34</u>
<u>509</u> ATP5C1, ATP5C	ADPm + Pim + 3 H $\rightarrow$ ATPm + 3 Hm + H2Om	<u>3.6.1.34</u>
<u>498</u> ATP5A1, ATP5A, ATPM, OMR, HATP1	ADPm + Pim + 3 H $\rightarrow$ ATPm + 3 Hm + H2Om	<u>3.6.1.34</u>
<u>539</u> ATP50, ATP0, OSCP	ADPm + Pim + 3 H $\rightarrow$ ATPm + 3 Hm + H2Om	<u>3.6.1.34</u>
<u>516</u> ATP5G1, ATP5G	ADPm + Pim + 3 H $\rightarrow$ ATPm + 3 Hm + H2Om	<u>3.6.1.34</u>
<u>517</u> ATP5G2	ADPm + Pim + 3 H $\rightarrow$ ATPm + 3 Hm + H2Om	<u>3.6.1.34</u>
<u>518</u> ATP5G3	ADPm + Pim + 3 H $\rightarrow$ ATPm + 3 Hm + H2Om	<u>3.6.1.34</u>
<u>515</u> ATP5F1	ADPm + Pim + 3 H $\rightarrow$ ATPm + 3 Hm + H2Om	<u>3.6.1.34</u>
<u>521</u> ATP5I	ADPm + Pim + 3 H $\rightarrow$ ATPm + 3 Hm + H2Om	<u>3.6.1.34</u>
<u>522</u> ATP5J, ATP5A, ATPM, ATP5	ADPm + Pim + 3 H $\rightarrow$ ATPm + 3 Hm + H2Om	<u>3.6.1.34</u>
<u>9551</u> ATP5J2, ATP5JL, F1FO-ATPASE	ADPm + Pim + 3 H $\rightarrow$ ATPm + 3 Hm + H2Om	<u>3.6.1.34</u>
<u>10476</u> ATP5JD	ADPm + Pim + 3 H $\rightarrow$ ATPm + 3 Hm + H2Om	<u>3.6.1.34</u>
<u>10632</u> ATP5JG	ADPm + Pim + 3 H $\rightarrow$ ATPm + 3 Hm + H2Om	<u>3.6.1.34</u>
<u>9296</u> ATP6S14	ADPm + Pim + 3 H $\rightarrow$ ATPm + 3 Hm + H2Om	<u>3.6.1.34</u>
<u>528</u> ATP6D	ADPm + Pim + 3 H $\rightarrow$ ATPm + 3 Hm + H2Om	<u>3.6.1.34</u>
<u>523</u> ATP6A1, VPP2	ADPm + Pim + 3 H $\rightarrow$ ATPm + 3 Hm + H2Om	<u>3.6.1.34</u>
<u>524</u> ATP6A2, VPP2	ADPm + Pim + 3 H $\rightarrow$ ATPm + 3 Hm + H2Om	<u>3.6.1.34</u>
<u>525</u> ATP6B1, VPP3, VATB	ADPm + Pim + 3 H $\rightarrow$ ATPm + 3 Hm + H2Om	<u>3.6.1.34</u>
<u>526</u> ATP6B2, VPP3	ADPm + Pim + 3 H $\rightarrow$ ATPm + 3 Hm + H2Om	<u>3.6.1.34</u>
<u>529</u> ATP6E	ADPm + Pim + 3 H $\rightarrow$ ATPm + 3 Hm + H2Om	<u>3.6.1.34</u>
<u>527</u> ATP6C, ATPL	ADPm + Pim + 3 H $\rightarrow$ ATPm + 3 Hm + H2Om	<u>3.6.1.34</u>
<u>533</u> ATP6F	ADPm + Pim + 3 H $\rightarrow$ ATPm + 3 Hm + H2Om	<u>3.6.1.34</u>
<u>10312</u> TCRG1, TIRC7, OC-116, OC-116kDa, OC-116KDA, ATP6N1C	ADPm + Pim + 3 H $\rightarrow$ ATPm + 3 Hm + H2Om	<u>3.6.1.34</u>
<u>23545</u> TJ6	ADPm + Pim + 3 H $\rightarrow$ ATPm + 3 Hm + H2Om	<u>3.6.1.34</u>
<u>50617</u> ATP6N1B	ADPm + Pim + 3 H $\rightarrow$ ATPm + 3 Hm + H2Om	<u>3.6.1.34</u>
<u>535</u> ATP6N1	ADPm + Pim + 3 H $\rightarrow$ ATPm + 3 Hm + H2Om	<u>3.6.1.34</u>
<u>51382</u> VATD	ADPm + Pim + 3 H $\rightarrow$ ATPm + 3 Hm + H2Om	<u>3.6.1.34</u>
<u>8992</u> ATP6H	ADPm + Pim + 3 H $\rightarrow$ ATPm + 3 Hm + H2Om	<u>3.6.1.34</u>
<u>9550</u> ATP6J	ADPm + Pim + 3 H $\rightarrow$ ATPm + 3 Hm + H2Om	<u>3.6.1.34</u>
<u>51606</u> LOC51606	ADPm + Pim + 3 H $\rightarrow$ ATPm + 3 Hm + H2Om	<u>3.6.1.34</u>
<u>495</u> ATP4A, ATP6A	ATP + H + Kxt + H2O $\leftrightarrow$ ADP + Pi + Hext + K	<u>3.6.1.36</u>
<u>496</u> ATP4B, ATP6B	ATP + H + Kxt + H2O $\leftrightarrow$ ADP + Pi + Hext + K	<u>3.6.1.36</u>
<u>476</u> ATP1A1	ATP + 3 NA + 2 Kxt + H2O $\leftrightarrow$ ADP + 3 Naxt + 2 K + Pi	<u>3.6.1.37</u>
<u>477</u> ATP1A2	ATP + 3 NA + 2 Kxt + H2O $\leftrightarrow$ ADP + 3 Naxt + 2 K + Pi	<u>3.6.1.37</u>
<u>478</u> ATP1A3	ATP + 3 NA + 2 Kxt + H2O $\leftrightarrow$ ADP + 3 Naxt + 2 K + Pi	<u>3.6.1.37</u>
<u>479</u> ATP1AL1	ATP + 3 NA + 2 Kxt + H2O $\leftrightarrow$ ADP + 3 Naxt + 2 K + Pi	<u>3.6.1.37</u>
<u>23439</u> ATP1B4	ATP + 3 NA + 2 Kxt + H2O $\leftrightarrow$ ADP + 3 Naxt + 2 K + Pi	<u>3.6.1.37</u>
<u>481</u> ATP1B1, ATP1B	ATP + 3 NA + 2 Kxt + H2O $\leftrightarrow$ ADP + 3 Naxt + 2 K + Pi	<u>3.6.1.37</u>
<u>482</u> ATP1B2, AMOG	ATP + 3 NA + 2 Kxt + H2O $\leftrightarrow$ ADP + 3 Naxt + 2 K + Pi	<u>3.6.1.37</u>
<u>483</u> ATP1B3	ATP + 3 NA + 2 Kxt + H2O $\leftrightarrow$ ADP + 3 Naxt + 2 K + Pi	<u>3.6.1.37</u>
<u>27032</u> ATP2C1, ATP2C1A, PMR1	ATP + 2 CA + H2O $\leftrightarrow$ ADP + Pi + 2 CAxt	<u>3.6.1.38</u>

<u>487</u> ATP2A1, SERCA1, ATP2A	ATP + 2 CA + H2O $\leftrightarrow$ ADP + Pi + 2 CAxt	<u>3.6.1.38</u>
<u>488</u> ATP2A2, ATP2B, SERCA2, DAR, DD	ATP + 2 CA + H2O $\leftrightarrow$ ADP + Pi + 2 CAxt	<u>3.6.1.38</u>
<u>489</u> ATP2A3, SERCA3	ATP + 2 CA + H2O $\leftrightarrow$ ADP + Pi + 2 CAxt	<u>3.6.1.38</u>
<u>490</u> ATP2B1, PMCA1	ATP + 2 CA + H2O $\leftrightarrow$ ADP + Pi + 2 CAxt	<u>3.6.1.38</u>
<u>491</u> ATP2B2, PMCA2	ATP + 2 CA + H2O $\leftrightarrow$ ADP + Pi + 2 CAxt	<u>3.6.1.38</u>
<u>492</u> ATP2B3, PMCA3	ATP + 2 CA + H2O $\leftrightarrow$ ADP + Pi + 2 CAxt	<u>3.6.1.38</u>
<u>493</u> ATP2B4, ATP2B2, PMCA4	ATP + 2 CA + H2O $\leftrightarrow$ ADP + Pi + 2 CAxt	<u>3.6.1.38</u>
<u>538</u> ATP7A, MK, MNK, OHS	ATP + H2O + Cu2+ $\rightarrow$ ADP + Pi + Cu2xt	<u>3.6.3.4</u>
<u>540</u> ATP7B, WND	ATP + H2O + Cu2+ $\rightarrow$ ADP + Pi + Cu2xt	<u>3.6.3.4</u>
<u>5454</u> PP, S1D6-8061	PPI $\rightarrow$ 2 Pi	<u>3.6.1.1</u>
<b>2.2</b> Photosynthesis PATH:hsa00195		
<b>2.3</b> Carbon fixation PATH:hsa00710		
<u>2805</u> GOT1	OAm + GLUm $\leftrightarrow$ ASPm + AKGm	<u>2.6.1.1</u>
<u>2806</u> GOT2	OA + GLU $\leftrightarrow$ ASP + AKG	<u>2.6.1.1</u>
<u>2875</u> GPT	PYR + GLU $\leftrightarrow$ AKG + ALA	<u>2.6.1.2</u>
<b>2.4</b> Reductive carboxylate cycle (CO2 fixation) PATH:hsa00720		
<b>2.5</b> Methane metabolism PATH:hsa00680		
<u>847</u> CAT	2 H2O2 $\rightarrow$ O2	<u>1.11.1.6</u>
<u>4025</u> LPO, SPO		<u>1.11.1.7</u>
<u>4353</u> MPO		<u>1.11.1.7</u>
<u>8288</u> EPX, EPX-PEN, EPO, EPP		<u>1.11.1.7</u>
<u>9588</u> KIAA0106, AOP2		<u>1.11.1.7</u>
<u>6470</u> SHMT1, CSHMT	THF + SER $\leftrightarrow$ GLY + METTHF	<u>2.1.2.1</u>
<u>6472</u> SHMT2, GLYA, SHMT	THFm + SERm $\leftrightarrow$ GLYm + METTHFm	<u>2.1.2.1</u>
<u>51004</u> LOC51004	2OPMPm + O2m $\rightarrow$ 2OPMBm	<u>1.14.13-</u>
	2OPMMBm + O2m $\rightarrow$ 2OMHMBm	
	2OPMPm + O2m $\rightarrow$ 2OPMBm	<u>1.14.13-</u>
	2OPMMBm + O2m $\rightarrow$ 2OMHMBm	
<b>2.6</b> Nitrogen metabolism PATH:hsa00910		
<u>11238</u> CA5B		<u>4.2.1.1</u>
<u>23632</u> CA14		<u>4.2.1.1</u>
<u>759</u> CA1		<u>4.2.1.1</u>
<u>760</u> CA2		<u>4.2.1.1</u>
<u>761</u> CA3, CAIII		<u>4.2.1.1</u>
<u>762</u> CA4, CAIV		<u>4.2.1.1</u>
<u>763</u> CA5A, CA5, CAV, CAVA		<u>4.2.1.1</u>
<u>765</u> CA6		<u>4.2.1.1</u>
<u>766</u> CA7		<u>4.2.1.1</u>
<u>767</u> CA8, CALS, CARP		<u>4.2.1.1</u>
<u>768</u> CA9, MN		<u>4.2.1.1</u>
<u>770</u> CA11, CARP2		<u>4.2.1.1</u>
<u>771</u> CA12		<u>4.2.1.1</u>
<u>1373</u> CPS1	GLUm + CO2m + 2 ATPm $\rightarrow$ 2 ADPm + 2 Pi + CAPm	<u>6.3.4.16</u>
	GLYm + THFm + NADm $\leftrightarrow$ METTHFm + NADHm + CO2m + NH3m	<u>2.1.2.10</u>
	HIS $\rightarrow$ NH3 + URO	
<u>3034</u> HAL, HSTD, HIS	AKGm + NADHm + NH3m $\leftrightarrow$ NADm + H2O + GLUm	<u>4.3.1.3</u>
<u>2746</u> GLUD1, GLUD	AKGm + NADPHm + NH3m $\leftrightarrow$ NADPm + H2O + GLUm	<u>14.1.3</u>
	AKGm + NADHm + NH3m $\leftrightarrow$ NADm + H2O + GLUm	
	AKGm + NADPHm + NH3m $\leftrightarrow$ NADPm + H2O + GLUm	
<u>8307</u> GLUD2	AKGm + NADHm + NH3m $\leftrightarrow$ NADPm + H2O + GLUm	<u>14.1.3</u>
	GLUm + NH3m + ATPm $\rightarrow$ GLNm + ADPm + Pi	<u>6.3.1.2</u>
<u>2752</u> GLUL, GLNS	GLN $\rightarrow$ GLU + NH3	<u>3.5.1.2</u>
<u>22842</u> KIAA0838	GLN $\rightarrow$ GLU + NH3	<u>3.5.1.2</u>
<u>27165</u> GA	GLNm $\rightarrow$ GLUm + NH3m	<u>3.5.1.2</u>
<u>2744</u> GLS	ASPM + ATPm + GLNm $\rightarrow$ GLUm + ASNm + AMPm + PPIm	<u>6.3.5.4</u>
<u>440</u> ASNS	LLCT + H2O $\rightarrow$ CYS + HSER	<u>4.4.1.1</u>
<u>1491</u> CTH	OBUT + NH3 $\leftrightarrow$ HSER	<u>4.4.1.1</u>
<b>2.7</b> Sulfur metabolism PATH:hsa00920		
<u>9060</u> PAPSS2, ATPSK2, SK2	APS + ATP $\rightarrow$ ADP + PAPS	<u>2.7.1.25</u>
	SLF + ATP $\rightarrow$ PPI + APS	<u>2.7.7.4</u>
<u>9061</u> PAPSS1, ATPSK1, SK1	APS + ATP $\rightarrow$ ADP + PAPS	<u>2.7.1.25</u>
	SLF + ATP $\rightarrow$ PPI + APS	<u>2.7.7.4</u>
<u>10380</u> BPNT1	PAP $\rightarrow$ AMP + Pi	<u>3.1.3.7</u>
<u>6799</u> SULT1A2		<u>2.8.2.1</u>
<u>6817</u> SULT1A1, STP1		<u>2.8.2.1</u>
<u>6818</u> SULT1A3, STM		<u>2.8.2.1</u>
<u>6822</u> SULT2A1, STD		<u>2.8.2.2</u>

6783 STE, EST	2.8.2.4	
6821 SUOX	<u>1.8.3.1</u>	
3. Lipid Metabolism		
3.1 Fatty acid biosynthesis (path 1) PATH:hsa00061		
2194 FASN	<u>2.3.1.85</u>	
3.2 Fatty acid biosynthesis (path 2) PATH:hsa00062		
10449 ACAA2, DSAEC	MAACOAm $\rightarrow$ ACCOAm + PROPCOAm	2.3.1.16
30 ACAA1, ACAA	MAACOA $\rightarrow$ ACCOA + PROPCOA	2.3.1.16
3032 HADHB	MAACOA $\rightarrow$ ACCOA + PROPCOA	2.3.1.16
3.3 Fatty acid metabolism PATH:hsa00071		
51 ACOX1, ACOX		1.3.3.6
33 ACADL, LCAD		<u>1.3.99.13</u>
2639 GCDH		<u>1.3.99.7</u>
2179 FACL1, LACS	ATP + LCCA + COA $\leftrightarrow$ AMP + PPI + ACOA	6.2.1.3
2180 FACL2, FACL1, LACS2	ATP + LCCA + COA $\leftrightarrow$ AMP + PPI + ACOA	6.2.1.3
2182 FACL4, ACS4	ATP + LCCA + COA $\leftrightarrow$ AMP + PPI + ACOA	6.2.1.3
1374 CPT1A, CPT1, CPT1-L		<u>2.3.1.21</u>
1375 CPT1B, CPT1-M		<u>2.3.1.21</u>
1376 CPT2, CPT1, CPTASE		<u>2.3.1.21</u>
1632 DCI		<u>5.3.3.8</u>
11283 CYP4F8		<u>1.14.14.1</u>
1543 CYP1A1, CYP1		<u>1.14.14.1</u>
1544 CYP1A2		<u>1.14.14.1</u>
1545 CYP1B1, GLC3A		<u>1.14.14.1</u>
1548 CYP2A6, CYP2A3		<u>1.14.14.1</u>
1549 CYP2A7		<u>1.14.14.1</u>
1551 CYP3A7		<u>1.14.14.1</u>
1553 CYP2A13		<u>1.14.14.1</u>
1554 CYP2B		<u>1.14.14.1</u>
1555 CYP2B6		<u>1.14.14.1</u>
1557 CYP2C19, CYP2C, P450IIC19		<u>1.14.14.1</u>
1558 CYP2C8		<u>1.14.14.1</u>
1559 CYP2C9, P450IIC9, CYP2C10		<u>1.14.14.1</u>
1562 CYP2C18, P450IIC17, CYP2C17		<u>1.14.14.1</u>
1565 CYP2D6		<u>1.14.14.1</u>
1571 CYP2E, CYP2E1, P450C2E		<u>1.14.14.1</u>
1572 CYP2F1, CYP2F		<u>1.14.14.1</u>
1573 CYP2J2		<u>1.14.14.1</u>
1575 CYP3A3		<u>1.14.14.1</u>
1576 CYP3A4		<u>1.14.14.1</u>
1577 CYP3A5, PCN3		<u>1.14.14.1</u>
1580 CYP4B1		<u>1.14.14.1</u>
1588 CYP19, ARO		<u>1.14.14.1</u>
1595 CYP51		<u>1.14.14.1</u>
194 AHHR, AHH		<u>1.14.14.1</u>
3.4 Synthesis and degradation of ketone bodies PATH:hsa00072		
3.5 Sterol biosynthesis PATH:hsa00100		
3156 HMGCR	MVL + COA + 2 NADP $\leftrightarrow$ H3MCOA + 2 NADPH	<u>1.1.1.34</u>
4598 MVK, MVLK	ATP + MVL $\rightarrow$ ADP + PMVL	<u>2.7.1.36</u>
	CTP + MVL $\rightarrow$ CDP + PMVL	
	GTP + MVL $\rightarrow$ GDP + PMVL	
	UTP + MVL $\rightarrow$ UDP + PMVL	
10654 PMVK, PMKASE, PMK, HUMPMKI	ATP + PMVL $\rightarrow$ ADP + PPMVL	<u>2.7.4.2</u>
4597 MVD, MPD	ATP + PPMVL $\rightarrow$ ADP + Pi + IPPP + CO2	<u>4.1.1.33</u>
3422 IDI1	IPPP $\leftrightarrow$ DMPP	<u>5.3.3.2</u>
2224 FDPS	GPP + IPPP $\rightarrow$ FPP + PPI	<u>2.5.1.10</u>
	DMPP + IPPP $\rightarrow$ GPP + PPI	<u>2.5.1.1</u>
9453 GGPS1, GGPPS	DMPP + IPPP $\rightarrow$ GPP + PPI	<u>2.5.1.10</u>
	GPP + IPPP $\rightarrow$ FPP + PPI	<u>2.5.1.29</u>
2222 FDFT1, DGPT	2 FPP + NADPH $\rightarrow$ NADP + SQL	<u>2.5.1.21</u>
6713 SQLE	SQL + O2 + NADP $\rightarrow$ S23E + NADPH	<u>1.14.99.7</u>
4047 LSS, OSC	S23E $\rightarrow$ LNST	<u>5.4.99.7</u>
1728 DIA4, NMOR1, NQO1, NMOR1		<u>1.6.99.2</u>
4835 NMOR2, NQO2		<u>1.6.99.2</u>
37 ACADVL, VLCAD, LCACD		<u>1.3.99.-</u>
3.6 Bile acid biosynthesis PATH:hsa00120		

<u>1056</u> CEL, BSSL, BAL	<u>3.1.1.3</u>
<u>3988</u> LIPA, LAL	<u>3.1.1.13</u>
<u>6646</u> SOAT1, ACAT, STAT, SOAT, ACAT1, <u>ACACT</u>	<u>3.1.1.13</u>
<u>1581</u> CYP7A1, CYP7	<u>1.14.13.17</u>
<u>6715</u> SRD5A1	<u>1.3.99.5</u>
<u>6716</u> SRD5A2	<u>1.3.99.5</u>
<u>6718</u> AKR1D1, SRD5B1, 3o5bred	<u>1.3.99.6</u>
<u>570</u> BAAT, BAT	<u>2.3.1.65</u>
3.7 C21-Steroid hormone metabolism PATH:hsa00140	
<u>1583</u> CYP11A, P450SCC	<u>1.14.15.6</u>
<u>3283</u> HSD3B1, HSD3B, HSDB3	<u>5.3.3.1</u>
IMZYMST $\rightarrow$ IIMZYMST + CO2	
IMZYMST $\rightarrow$ IIZYMST + CO2	
<u>3284</u> HSD3B2	<u>1.1.1.145</u>
IMZYMST $\rightarrow$ IIMZYMST + CO2	
IMZYMST $\rightarrow$ IIZYMST + CO2	
<u>1589</u> CYP21A2, CYP21, P450C21B, <u>1589</u> CA21H, CYP21B, P450c21B	<u>1.14.99.10</u>
<u>1586</u> CYP17, P450C17	<u>1.14.99.9</u>
<u>1584</u> CYP11B1, P450C11, CYP11B	<u>1.14.15.4</u>
<u>1585</u> CYP11B2, CYP11B	<u>1.14.15.4</u>
<u>3290</u> HSD11B1, HSD11, HSD11L, HSD11B	<u>1.1.1.146</u>
<u>3291</u> HSD11B2, HSD11K	<u>1.1.1.146</u>
3.8 Androgen and estrogen metabolism PATH:hsa00150	
<u>3292</u> HSD17B1, EDH17B2, EDHB17, <u>3292</u> HSD17	<u>1.1.1.62</u>
<u>3293</u> HSD17B3, EDH17B3	<u>1.1.1.62</u>
<u>3294</u> HSD17B2, EDH17B2	<u>1.1.1.62</u>
<u>3295</u> HSD17B4	<u>1.1.1.62</u>
<u>3296</u> HSD17B1, EDH17B1, EDHB17, <u>3296</u> HSD17	<u>1.1.1.62</u>
<u>51478</u> HSD17B7, PRAP	<u>1.1.1.62</u>
<u>412</u> STS, ARSC, ARSC1, SSDD	<u>3.1.6.2</u>
<u>414</u> ARSD	<u>3.1.6.1</u>
<u>415</u> ARSE, CDPX1, CDPXR, CDPX	<u>3.1.6.1</u>
<u>11185</u> INMT	<u>2.1.1-</u>
<u>24140</u> JM23	<u>2.1.1-</u>
<u>29104</u> N6AMT1, PRED28	<u>2.1.1-</u>
<u>29960</u> FJH1	<u>2.1.1-</u>
<u>3276</u> HRMT1L2, HCP1, PRMT1	<u>2.1.1-</u>
<u>51628</u> LOC51628	<u>2.1.1-</u>
<u>54743</u> HASJ4442	<u>2.1.1-</u>
<u>27292</u> HSA9761	<u>2.1.1-</u>
4. Nucleotide Metabolism	
4.1 Purine metabolism PATH:hsa00230	
<u>11164</u> NUDT5, HYSAH1, YSA1H	<u>3.6.1.13</u>
<u>5471</u> PPAT, GPAT	<u>2.4.2.14</u>
<u>2618</u> GART, PGFT, PRGS	<u>6.3.4.13</u>
PRPP + GLN $\rightarrow$ PPI + GLU + PRAM	
PRAM + ATP + GLY $\leftrightarrow$ ADP + PI + GAR	
FGAM + ATP $\rightarrow$ ADP + PI + AIR	
GAR + FTHF $\rightarrow$ THF + FGAR	
FGAR + ATP + GLN $\rightarrow$ GLU + ADP + PI + FGAM	
CAIR + ATP + ASP $\leftrightarrow$ ADP + PI + SAICAR	
CAIR $\leftrightarrow$ AIR + CO2	
CAIR + ATP + ASP $\leftrightarrow$ ADP + PI + SAICAR	
ASUC $\leftrightarrow$ FJU + AMP	
AICAR + FTHF $\leftrightarrow$ THF + PRFICA	
PRFICA $\leftrightarrow$ IMP	
HYXAN + PRPP $\rightarrow$ PPI + IMP	
GN + PRPP $\rightarrow$ PPI + GMP	
IMP + NAD $\rightarrow$ NADH + XMP	
IMP + NAD $\rightarrow$ NADH + XMP	
<u>5198</u> PFAS, FGARAT, KIAA0361, PURL	<u>6.3.5.3</u>
<u>10606</u> ADE2H1	<u>6.3.2.6</u>
<u>5059</u> PAICS, AIRC, PAIS	<u>4.1.1.21</u>
<u>158</u> ADSL	<u>6.3.2.6</u>
<u>471</u> ATIC, PURH	<u>4.3.2.2</u>
<u>3251</u> HPRT1, HPRT, HGPRT	<u>2.1.2.3</u>
HYXAN + PRPP $\rightarrow$ PPI + IMP	
GN + PRPP $\rightarrow$ PPI + GMP	
IMP + NAD $\rightarrow$ NADH + XMP	
IMP + NAD $\rightarrow$ NADH + XMP	
<u>3614</u> IMPDH1	<u>3.5.4.10</u>
<u>3615</u> IMPDH2	<u>2.4.2.8</u>
<u>8833</u> GMPS	<u>1.1.1.205</u>
<u>14923</u>	<u>1.1.1.205</u>
<u>2987</u> GUK1	<u>6.3.5.2</u>
GMP + ATP $\leftrightarrow$ GDP + ADP	
	<u>2.7.4.8</u>

<u>2988</u> GUK2	DGMP + ATP $\leftrightarrow$ DGDP + ADP GMP + DATP $\leftrightarrow$ GDP + DADP GMP + ATP $\leftrightarrow$ GDP + ADP DGMP + ATP $\leftrightarrow$ DGDP + ADP GMP + DATP $\leftrightarrow$ GDP + DADP	<u>2.7.4.8</u>
<u>10621</u> RPC39		<u>2.7.7.6</u>
<u>10622</u> RPC32		<u>2.7.7.6</u>
<u>10623</u> RPC62		<u>2.7.7.6</u>
<u>11128</u> RPC155		<u>2.7.7.6</u>
<u>25885</u> DKFZP586M0122		<u>2.7.7.6</u>
<u>30834</u> ZNRD1		<u>2.7.7.6</u>
<u>51082</u> LOC51082		<u>2.7.7.6</u>
<u>51728</u> LOC51728		<u>2.7.7.6</u>
<u>5430</u> POLR2A, RPOL2, POLR2, POLRA		<u>2.7.7.6</u>
<u>5431</u> POLR2B, POL2RB		<u>2.7.7.6</u>
<u>5432</u> POLR2C		<u>2.7.7.6</u>
<u>5433</u> POLR2D, HSRBP4, HSRPB4		<u>2.7.7.6</u>
<u>5434</u> POLR2E, RPB5, XAP4		<u>2.7.7.6</u>
<u>5435</u> POLR2F, RPB6, HRBP14.4		<u>2.7.7.6</u>
<u>5436</u> POLR2G, RPB7		<u>2.7.7.6</u>
<u>5437</u> POLR2H, RPB8, RPB17		<u>2.7.7.6</u>
<u>5438</u> POLR2I		<u>2.7.7.6</u>
<u>5439</u> POLR2J		<u>2.7.7.6</u>
<u>5440</u> POLR2K, RPB7.0		<u>2.7.7.6</u>
<u>5441</u> POLR2L, RPB7.6, RPB10		<u>2.7.7.6</u>
<u>5442</u> POLRMT, APOLMT		<u>2.7.7.6</u>
<u>54479</u> FLJ10816, Rpo1-2		<u>2.7.7.6</u>
<u>55703</u> FLJ10388		<u>2.7.7.6</u>
<u>661</u> BN51T		<u>2.7.7.6</u>
<u>9533</u> RPA40, RPA39		<u>2.7.7.7</u>
<u>10721</u> POLQ		<u>2.7.7.7</u>
<u>11232</u> POLG2, MTPOLB, HP55, POLB		<u>2.7.7.7</u>
<u>23649</u> POLA2		<u>2.7.7.7</u>
<u>5422</u> POLA		<u>2.7.7.7</u>
<u>5423</u> POLB		<u>2.7.7.7</u>
<u>5424</u> POLD1, POLD		<u>2.7.7.7</u>
<u>5425</u> POLD2		<u>2.7.7.7</u>
<u>5426</u> POLE		<u>2.7.7.7</u>
<u>5427</u> POLE2		<u>2.7.7.7</u>
<u>5428</u> POLG		<u>2.7.7.7</u>
<u>5980</u> REV3L, POLZ, REV3		<u>1.1.3.22</u>
<u>7498</u> XDH		<u>1.1.1.204</u>
<u>9615</u> GDA, KIAA1258, CYPIN, NEDASIN		<u>3.5.4.3</u>
<u>2766</u> GMPR		<u>1.6.6.8</u>
<u>51292</u> LOC51292		<u>1.6.6.8</u>
<u>7377</u> UOX		<u>1.7.3.3</u>
<u>6240</u> RRM1	ADP + RTHIO $\rightarrow$ DADP + OTHIO GDP + RTHIO $\rightarrow$ DGDP + OTHIO CDP + RTHIO $\rightarrow$ DCDP + OTHIO UDP + RTHIO $\rightarrow$ DUDP + OTHIO ADP + RTHIO $\rightarrow$ DADP + OTHIO	<u>1.17.4.1</u>
<u>6241</u> RRM2	GDP + RTHIO $\rightarrow$ DGDP + OTHIO CDP + RTHIO $\rightarrow$ DCDP + OTHIO UDP + RTHIO $\rightarrow$ DUDP + OTHIO	<u>1.17.4.1</u>
<u>4860</u> NP, PNP	AND + PI $\leftrightarrow$ AD + R1P GSN + PI $\leftrightarrow$ GN + R1P DA + PI $\leftrightarrow$ AD + R1P DG + PI $\leftrightarrow$ GN + R1P DIN + PI $\leftrightarrow$ HYXAN + R1P INS + PI $\leftrightarrow$ HYXAN + R1P XTSINE + PI $\leftrightarrow$ XAN + R1P DU + PI $\leftrightarrow$ URA + DR1P DT + PI $\leftrightarrow$ THY + DR1P AD + PRPP $\rightarrow$ PPI + AMP ADN + ATP $\rightarrow$ AMP + ADP	<u>2.4.2.1</u>
<u>1890</u> ECGF1, hPD-ECGF		<u>2.4.2.4</u>
<u>353</u> APRT		<u>2.4.2.7</u>
<u>132</u> ADK		<u>2.7.1.20</u>
<u>1633</u> DCK		<u>2.7.1.74</u>

<u>1716</u> DGUOK	ATP + AMP <=> 2 ADP	<u>2.7.1.113</u>
<u>203</u> AK1	GTP + AMP <=> ADP + GDP	<u>2.7.4.3</u>
	ITP + AMP <=> ADP + IDP	
<u>204</u> AK2	ATP + AMP <=> 2 ADP	<u>2.7.4.3</u>
	GTP + AMP <=> ADP + GDP	
	ITP + AMP <=> ADP + IDP	
<u>205</u> AK3	ATP + AMP <=> 2 ADP	<u>2.7.4.3</u>
	GTP + AMP <=> ADP + GDP	
	ITP + AMP <=> ADP + IDP	
<u>26289</u> AK5	ATP + AMP <=> 2 ADP	<u>2.7.4.3</u>
	GTP + AMP <=> ADP + GDP	
	ITP + AMP <=> ADP + IDP	
<u>4830</u> NME1, NM23, NM23-H1	UDP + ATP <=> UTP + ADP	<u>2.7.4.6</u>
	CDP + ATP <=> CTP + ADP	
	GDP + ATP <=> GTP + ADP	
	IDP + ATP <=> ITP + IDP	
	DGDP + ATP <=> DGTP + ADP	
	DUDP + ATP <=> DUTP + ADP	
	DCDP + ATP <=> DCTP + ADP	
	DTDP + ATP <=> DTTP + ADP	
	DADP + ATP <=> DATP + ADP	
<u>4831</u> NME2, NM23-H2	UDP + ATP <=> UTP + ADP	<u>2.7.4.6</u>
	CDP + ATP <=> CTP + ADP	
	GDP + ATP <=> GTP + ADP	
	IDP + ATP <=> ITP + IDP	
	DGDP + ATP <=> DGTP + ADP	
	DUDP + ATP <=> DUTP + ADP	
	DCDP + ATP <=> DCTP + ADP	
	DTDP + ATP <=> DTTP + ADP	
	DADP + ATP <=> DATP + ADP	
<u>4832</u> NME3, DR-nm23, DR-NM23	UDP + ATP <=> UTP + ADP	<u>2.7.4.6</u>
	CDP + ATP <=> CTP + ADP	
	GDP + ATP <=> GTP + ADP	
	IDP + ATP <=> ITP + IDP	
	DGDP + ATP <=> DGTP + ADP	
	DUDP + ATP <=> DUTP + ADP	
	DCDP + ATP <=> DCTP + ADP	
	DTDP + ATP <=> DTTP + ADP	
	DADP + ATP <=> DATP + ADP	
<u>4833</u> NME4	UDPm + ATPm <=> UTPm + ADPm	<u>2.7.4.6</u>
	CDPm + ATPm <=> CTPm + ADPm	
	GDPm + ATPm <=> GTPm + ADPm	
	IDPm + ATPm <=> ITPm + IDPm	
	DGDPm + ATPm <=> DGTPm + ADPm	
	DUDPm + ATPm <=> DUTPm + ADPm	
	DCDPm + ATPm <=> DCTPm + ADPm	
	DTDPm + ATPm <=> DTTPm + ADPm	
	DADPm + ATPm <=> DATPm + ADPm	
<u>22978</u> NT5B, PNT5, NT5B-PENDING	AMP + H2O → PI + ADN	<u>3.1.3.5</u>
	GMP → PI + GSN	
	CMP → CYTD + PI	
	UMP → PI + URI	
	IMP → PI + INS	
	DUMP → DU + PI	
	DTMP → DT + PI	
	DAMP → DA + PI	
	DGMP → DG + PI	
	DCMP → DC + PI	
	XMP → PI + XTSINE	
<u>4877</u> NT3	AMP → PI + ADN	<u>3.1.3.5</u>
	GMP → PI + GSN	
	CMP → CYTD + PI	
	UMP → PI + URI	
	IMP → PI + INS	
	DUMP → DU + PI	
	DTMP → DT + PI	

	DAMP $\rightarrow$ DA + PI	
	DGMP $\rightarrow$ DG + PI	
	DCMP $\rightarrow$ DC + PI	
	XMP $\rightarrow$ PI + XTSINE	
<u>4907</u> NT5, CD73	AMP $\rightarrow$ PI + ADN	<u>3.1.3.5</u>
	GMP $\rightarrow$ PI + GSN	
	CMP $\rightarrow$ CYTD + PI	
	UMP $\rightarrow$ PI + URI	
	IMP $\rightarrow$ PI + INS	
	DUMP $\rightarrow$ DU + PI	
	DTMP $\rightarrow$ DT + PI	
	DAMP $\rightarrow$ DA + PI	
	DGMP $\rightarrow$ DG + PI	
	DCMP $\rightarrow$ DC + PI	
	XMP $\rightarrow$ PI + XTSINE	
<u>7370</u> UMPH2	AMP $\rightarrow$ PI + ADN	<u>3.1.3.5</u>
	GMP $\rightarrow$ PI + GSN	
	CMP $\rightarrow$ CYTD + PI	
	UMP $\rightarrow$ PI + URI	
	IMP $\rightarrow$ PI + INS	
	DUMP $\rightarrow$ DU + PI	
	DTMP $\rightarrow$ DT + PI	
	DAMP $\rightarrow$ DA + PI	
	DGMP $\rightarrow$ DG + PI	
	DCMP $\rightarrow$ DC + PI	
	XMP $\rightarrow$ PI + XTSINE	
<u>10846</u> PDE10A	cAMP $\rightarrow$ AMP	<u>3.1.4.17</u>
	cAMP $\rightarrow$ AMP	
	cdAMP $\rightarrow$ dAMP	
	cIMP $\rightarrow$ IMP	
	cGMP $\rightarrow$ GMP	
	cCMP $\rightarrow$ CMP	
	cAMP $\rightarrow$ AMP	
<u>27115</u> PDE7B	cAMP $\rightarrow$ AMP	<u>3.1.4.17</u>
	cdAMP $\rightarrow$ dAMP	
	cIMP $\rightarrow$ IMP	
	cGMP $\rightarrow$ GMP	
	cCMP $\rightarrow$ CMP	
<u>5136</u> PDE1A	cAMP $\rightarrow$ AMP	<u>3.1.4.17</u>
	cdAMP $\rightarrow$ dAMP	
	cIMP $\rightarrow$ IMP	
	cGMP $\rightarrow$ GMP	
	cCMP $\rightarrow$ CMP	
<u>5137</u> PDE1C, HCAM3	cAMP $\rightarrow$ AMP	<u>3.1.4.17</u>
	cdAMP $\rightarrow$ dAMP	
	cIMP $\rightarrow$ IMP	
	cGMP $\rightarrow$ GMP	
	cCMP $\rightarrow$ CMP	
<u>5138</u> PDE2A	cAMP $\rightarrow$ AMP	<u>3.1.4.17</u>
	cdAMP $\rightarrow$ dAMP	
	cIMP $\rightarrow$ IMP	
	cGMP $\rightarrow$ GMP	
	cCMP $\rightarrow$ CMP	
<u>5139</u> PDE3A, CGI-PDE	cAMP $\rightarrow$ AMP	<u>3.1.4.17</u>
	cdAMP $\rightarrow$ dAMP	
	cIMP $\rightarrow$ IMP	
	cGMP $\rightarrow$ GMP	
	cCMP $\rightarrow$ CMP	
<u>5140</u> PDE3B	cAMP $\rightarrow$ AMP	<u>3.1.4.17</u>
	cdAMP $\rightarrow$ dAMP	
	cIMP $\rightarrow$ IMP	
	cGMP $\rightarrow$ GMP	

	cCMP → CMP	
<u>5141</u> PDE4A, DPDE2	cAMP → AMP	<u>3.1.4.17</u>
<u>5142</u> PDE4B, DPDE4, PDEIVB	cAMP → AMP	<u>3.1.4.17</u>
<u>5143</u> PDE4C, DPDE1	cAMP → AMP	<u>3.1.4.17</u>
<u>5144</u> PDE4D, DPDE3	cAMP → AMP	<u>3.1.4.17</u>
<u>5145</u> PDE6A, PDEA, CGPR-A	cGMP → GMP	<u>3.1.4.17</u>
<u>5146</u> PDE6C, PDEA2	cGMP → GMP	<u>3.1.4.17</u>
<u>5147</u> PDE6D	cGMP → GMP	<u>3.1.4.17</u>
<u>5148</u> PDE6G, PDEG	cGMP → GMP	<u>3.1.4.17</u>
<u>5149</u> PDE6H	cGMP → GMP	<u>3.1.4.17</u>
<u>5152</u> PDE9A	cAMP → AMP	<u>3.1.4.17</u>
	cAMP → AMP	
	cdAMP → dAMP	
	cIMP → IMP	
	cGMP → GMP	
	cCMP → CMP	
<u>5153</u> PDES1B	cAMP → AMP	<u>3.1.4.17</u>
	cAMP → AMP	
	cdAMP → dAMP	
	cIMP → IMP	
	cGMP → GMP	
	cCMP → CMP	
<u>5158</u> PDE6B, CSNB3, PDEB	cGMP → GMP	<u>3.1.4.17</u>
<u>8654</u> PDE5A	cGMP → GMP	<u>3.1.4.17</u>
<u>100</u> ADA	ADN → INS + NH3	<u>3.5.4.4</u>
	DA → DIN + NH3	
<u>270</u> AMPD1, MADA	AMP → IMP + NH3	<u>3.5.4.6</u>
<u>271</u> AMPD2	AMP → IMP + NH3	<u>3.5.4.6</u>
<u>272</u> AMPD3	AMP → IMP + NH3	<u>3.5.4.6</u>
<u>953</u> ENTPD1, CD39		<u>3.6.1.5</u>
<u>3704</u> ITPA		<u>3.6.1.19</u>
<u>107</u> ADCY1	ATP → cAMP + PPI	<u>4.6.1.1</u>
<u>108</u> ADCY2, HBAC2	ATP → cAMP + PPI	<u>4.6.1.1</u>
<u>109</u> ADCY3, AC3, KIAA0511	ATP → cAMP + PPI	<u>4.6.1.1</u>
<u>110</u> ADCY4	ATP → cAMP + PPI	<u>4.6.1.1</u>
<u>111</u> ADCY5	ATP → cAMP + PPI	<u>4.6.1.1</u>
<u>112</u> ADCY6	ATP → cAMP + PPI	<u>4.6.1.1</u>
<u>113</u> ADCY7, KIAA0037	ATP → cAMP + PPI	<u>4.6.1.1</u>
<u>114</u> ADCY8, ADCY3, HBAC1	ATP → cAMP + PPI	<u>4.6.1.1</u>
<u>115</u> ADCY9	ATP → cAMP + PPI	<u>4.6.1.1</u>
<u>2977</u> GUCY1A2, GUC1A2, GC-SA2		<u>4.6.1.2</u>
	GUCY1A3, GUC1A3, GUCSA3, GC-	
<u>2982</u> SA3		<u>4.6.1.2</u>
	GUCY1B3, GUC1B3, GUCSB3, GC-	
<u>2983</u> SB3		<u>4.6.1.2</u>
<u>2984</u> GUCY2C, GUC2C, STAR		<u>4.6.1.2</u>
	GUCY2F, GUC2F, GC-F, GUC2DL,	
<u>2986</u> RETGC-2		<u>4.6.1.2</u>
	GUCY2D, CORD6, GUC2D, LCA1,	
<u>3000</u> GUC1A4, LCA, retGC		<u>4.6.1.2</u>
<u>4881</u> NPR1, ANPRA, GUC2A, NPRA		<u>4.6.1.2</u>
	NPR2, ANPRB, GUC2B, NPRB,	
<u>4882</u> NPRBI		<u>4.6.1.2</u>
<u>159</u> ADSS	IMP + GTP + ASP → GDP + PI + ASUC	<u>6.3.4.4</u>
<u>318</u> NUDT2, APAH1		<u>3.6.1.17</u>
	ENPP1, M6S1, NPPS, PCA1, PC-1,	
<u>5167</u> PDNP1		<u>3.6.1.9</u>
<u>5168</u> ENPP2, ATX, PD-ALPHA, PDNP2		<u>3.6.1.9</u>
<u>5169</u> ENPP3, PD-IBETA, PDNP3		<u>3.6.1.9</u>
		<u>3.1.4.1</u>
		<u>3.6.1.29</u>
<u>2272</u> FHIT		
4.2 Pyrimidine metabolism PATH:hsa00240		
<u>790</u> CAD	GLN + 2 ATP + CO2 → GLU + CAP + 2 ADP + PI	<u>6.3.5.5</u>
	CAP + ASP → CAASP + PI	<u>2.1.3.2</u>
	CAASP ↔ DOROA	<u>3.5.2.3</u>
<u>1723</u> DHODH	DOROA + O2 ↔ H2O2 + OROA	<u>1.3.3.1</u>
<u>7372</u> UMPS, OPRT	OMP → CO2 + UMP	<u>4.1.1.23</u>

<u>51727 LOC51727</u>	OROA + PRPP $\leftrightarrow$ PPI + OMP ATP + UMP $\leftrightarrow$ ADP + UDP CMP + ATP $\leftrightarrow$ ADP + CDP DCMP + ATP $\leftrightarrow$ ADP + DCDP	<u>2.4.2.10</u> <u>2.7.4.14</u> <u>2.7.4.10</u> <u>6.3.4.2</u>
<u>50808 AKL3L</u> <u>1503 CTPS</u>	UTP + GLN + ATP $\rightarrow$ GLU + CTP + ADP + Pi ATP + UTP + NH3 $\rightarrow$ ADP + Pi + CTP	<u>2.7.1.48</u>
<u>7371 UMPK, TSA903</u>	URI + ATP $\rightarrow$ ADP + UMP URI + GTP $\rightarrow$ UMP + GDP CYTD + GTP $\rightarrow$ GDP + CMP URI + Pi $\leftrightarrow$ URA + R1P	<u>2.4.2.3</u> <u>1.3.1.2</u> <u>3.5.2.2</u> <u>3.5.1.6</u>
<u>7378 UP</u> <u>1806 DPYD, DPD</u> <u>1807 DPYS, DHPase, DHPASE, DHP</u>		<u>1.6.4.5</u> <u>3.6.1.23</u> <u>2.1.1.45</u> <u>3.5.4.5</u>
<u>51733 LOC51733</u> <u>7296 TXNRD1, TXNR</u> <u>1854 DUT</u> <u>7298 TYMS, TMS, TS</u> <u>978 CDA, CDD</u>	OTHIO + NADPH $\rightarrow$ NADP + RTHIO DUTP $\rightarrow$ PPI + DUMP DUMP + METTHF $\rightarrow$ DHF + DTMP CYTD $\rightarrow$ URI + NH3 DC $\rightarrow$ NH3 + DU DCMP $\leftrightarrow$ DUMP + NH3 DU + ATP $\rightarrow$ DUMP + ADP DT + ATP $\rightarrow$ ADP + DTMP DUM + ATPm $\rightarrow$ DUMPm + ADPm DTm + ATPm $\rightarrow$ ADPm + DTMPm DTMP + ATP $\leftrightarrow$ ADP + DTDP	<u>3.5.4.12</u> <u>2.7.1.21</u> <u>2.7.1.21</u> <u>2.7.4.9</u>
<u>1635 DCTD</u> <u>7083 TK1</u>		<u>4.2.1.46</u> <u>3.2.1.-</u>
<u>7084 TK2</u>		
<u>1841 DTYMK, TYMK, CDC8</u>		
<b>4.3 Nucleotide sugars metabolism PATH:hsa00520</b>		
<u>23483 TDPGD</u> <u>1486 CTBS, CTB</u>		
<b>5. Amino Acid Metabolism</b>		
<b>5.1 Glutamate metabolism PATH:hsa00251</b>		
<u>8659 ALDH4, P5CDH</u> <u>2058 EPRS, QARS, QPRS</u>	P5C + NAD + H2O $\rightarrow$ NADH + GLU GLU + ATP $\rightarrow$ GTRNA + AMP + PPI	<u>1.5.1.12</u> <u>6.1.1.17</u> <u>6.1.1.15</u>
<u>2673 GFPT1, GFA, GFAT, GFPT</u> <u>9945 GFPT2, GFAT2</u>	F6P + GLN $\rightarrow$ GLU + GA6P F6P + GLN $\rightarrow$ GLU + GA6P	<u>2.6.1.16</u> <u>2.6.1.16</u> <u>6.1.1.18</u>
<u>5859 QARS</u> <u>2729 GLCLC, GCS, GLCL</u> <u>2730 GLCLR</u> <u>2937 GSS, GSHS</u> <u>2936 GSR</u> <u>5188 PET112L, PET112</u>	CYS + GLU + ATP $\rightarrow$ GC + Pi + ADP CYS + GLU + ATP $\rightarrow$ GC + Pi + ADP GLY + GC + ATP $\rightarrow$ RGT + Pi + ADP NADPH + OGT $\rightarrow$ NADP + RGT	<u>6.3.2.2</u> <u>6.3.2.2</u> <u>6.3.2.3</u> <u>1.6.4.2</u> <u>6.3.5.-</u>
<b>5.2 Alanine and aspartate metabolism PATH:hsa00252</b>		
<u>4677 NARS, ASNRS</u> <u>435 ASL</u> <u>189 AGXT, SPAT</u>	ATP + ASP + TRNA $\rightarrow$ AMP + PPI + ASPTRNA ARGSUCC $\rightarrow$ FUM + ARG SERm + PYRm $\leftrightarrow$ ALAm + 3HPm ALA + GLX $\leftrightarrow$ PYR + GLY	<u>6.1.1.22</u> <u>4.3.2.1</u> <u>2.6.1.51</u> <u>2.6.1.44</u> <u>6.1.1.7</u>
<u>16 AARS</u> <u>1615 DARS</u>		<u>6.1.1.12</u> <u>6.3.4.5</u>
<u>445 ASS, CTLN1, ASS1</u> <u>443 ASPA, ASP, ACY2</u> <u>1384 CRAT, CAT1</u>	CITR + ASP + ATP $\leftrightarrow$ AMP + PPI + ARGSUCC ACCOA + CAR $\rightarrow$ COA + ACAR	<u>3.5.1.15</u> <u>2.3.1.7</u> <u>14.3.1</u>
<u>8528 DDO</u>		
<b>5.3 Glycine, serine and threonine metabolism PATH:hsa00260</b>		
<u>5723 PSPH, PSP</u> <u>29968 PSA</u>	3PSER + H2O $\rightarrow$ Pi + SER PHP + GLU $\leftrightarrow$ AKG + 3PSER OHB + GLU $\leftrightarrow$ PHT + AKG	<u>3.1.3.3</u> <u>2.6.1.52</u> <u>1.1.1.95</u>
<u>26227 PHGDH, SERA, PGDH, PGD, PGAD</u> <u>23464 GCAT, KBL</u>	3PG + NAD $\leftrightarrow$ NADH + PHP	<u>2.3.1.29</u> <u>2.3.1.37</u>
<u>211 ALAS1, ALAS</u> <u>212 ALAS2, ANH1, ASB</u>	SUCCOA + GLY $\rightarrow$ ALAV + COA + CO2 SUCCOA + GLY $\rightarrow$ ALAV + COA + CO2	<u>2.3.1.37</u> <u>14.3.4</u>
<u>4128 MAOA</u> <u>4129 MAOB</u>	AMA + H2O + FAD $\rightarrow$ NH3 + FADH2 + MTHGXL AMA + H2O + FAD $\rightarrow$ NH3 + FADH2 + MTHGXL	<u>14.3.4</u> <u>14.3.6</u>
<u>26 ABP1, AOC1, DAO</u> <u>314 AOC2, DAO2, RAO</u>		<u>14.3.6</u> <u>14.3.6</u>
<u>8639 AOC3, VAP-1, VAP1, HPAO</u> <u>2731 GLDC</u>	GLY + LIPO $\leftrightarrow$ SAP + CO2	<u>14.4.2</u>

<u>1610</u> DAO, DAMOX		<u>14.3.3</u>
<u>2617</u> GARS		<u>6.1.1.14</u>
<u>2628</u> GATM		<u>2.1.4.1</u>
<u>2593</u> GAMT		<u>2.1.1.2</u>
PISD, PSSC, DKFZP566G2246, <u>23761</u> DJ858B16	PS -> PE + CO2	<u>4.1.1.65</u>
<u>635</u> BHMT		<u>2.1.1.5</u>
<u>29958</u> DMGDH		<u>1.5.99.2</u>
<u>875</u> CBS	SER + HCYS -> LLCT + H2O	<u>4.2.1.22</u>
<u>6301</u> SARS, SERS		<u>6.1.1.11</u>
<u>10993</u> SDS, SDH	SER -> PYR + NH3 + H2O	<u>4.2.1.13</u>
<u>6897</u> TARS		<u>6.1.1.3</u>
<b>5.4</b> Methionine metabolism PATH:hsa00271		
<u>4143</u> MAT1A, MATA1, SAMS1, MAT, SAMS	MET + ATP + H2O -> PPI + PI + SAM	<u>2.5.1.6</u>
<u>4144</u> MAT2A, MATA2, SAMS2, MATII	MET + ATP + H2O -> PPI + PI + SAM	<u>2.5.1.6</u>
<u>1786</u> DNMT1, MCMT, DNMT	SAM + DNA -> SAH + DNA5MC	<u>2.1.1.37</u>
<u>10768</u> AHCYL1, XPVKONA	SAH + H2O -> HCYS + ADN	<u>3.3.1.1</u>
<u>191</u> AHCY, SAHH	SAH + H2O -> HCYS + ADN	<u>3.3.1.1</u>
<u>4141</u> MARS, METRS, MTRNS		<u>6.1.1.10</u>
<u>4548</u> MTR	HCYS + MTHF -> THF + MET	<u>2.1.1.13</u>
<b>5.5</b> Cysteine metabolism PATH:hsa00272		
<u>833</u> CARS		<u>6.1.1.16</u>
<u>1036</u> CDO1	CYS + O2 -> CYSS	<u>1.13.11.20</u>
<u>8509</u> NDST2, HSST2, NST2		<u>2.8.2.-</u>
<b>5.6</b> Valine, leucine and isoleucine degradation PATH:hsa00280		
<u>586</u> BCAT1, BCT1, ECA39, MECA39	AKG + ILE -> OMVAL + GLU	<u>2.6.1.42</u>
	AKG + VAL -> OIVAL + GLU	
	AKG + LEU -> OICAP + GLU	
<u>587</u> BCAT2, BCT2	OICAPm + GLUm -> AKGm + LEUm	<u>2.6.1.42</u>
	OMVALm + GLUm -> AKGm + ILEM	
<u>5014</u> OVD1A		<u>1.2.4.4</u>
<u>593</u> BCKDHA, MSUD1	OMVALm + COAm + NADm -> MBCOAm + NADHm + CO2m	<u>1.2.4.4</u>
	OIVALm + COAm + NADm -> IBCOAm + NADHm + CO2m	
	OICAPm + COAm + NADm -> IVCOAm + NADHm + CO2m	
<u>594</u> BCKDHB, E1B	OMVALm + COAm + NADm -> MBCOAm + NADHm + CO2m	<u>1.2.4.4</u>
	OIVALm + COAm + NADm -> IBCOAm + NADHm + CO2m	
	OICAPm + COAm + NADH -> IVCOAm + NADHm + CO2m	
<u>3712</u> IVD	IVCOAm + FADm -> MRCOAm + FADH2m	<u>1.3.99.10</u>
<u>316</u> AOX1, AO		<u>12.3.1</u>
<u>4164</u> MCCC1	MRCOAm + ATPm + CO2m + H2O m -> MGCOAm + ADPm + Pim	<u>6.4.1.4</u>
<u>4165</u> MCCC2	MRCOAm + ATPm + CO2m + H2O m -> MGCOAm + ADPm + Pim	<u>6.4.1.4</u>
<b>5.7</b> Valine, leucine and isoleucine biosynthesis PATH:hsa00290		
<u>23395</u> KIAA0028, LARS2		<u>6.4.1.4</u>
<u>3926</u> LARS		<u>6.4.1.4</u>
<u>3376</u> IARS, ILRS		<u>6.1.1.5</u>
<u>7406</u> VARS1, VARS		<u>6.1.1.9</u>
<u>7407</u> VARS2, G7A		<u>6.1.1.9</u>
<b>5.8</b> Lysine biosynthesis PATH:hsa00300		
<u>3735</u> KARS, KIAA0070	ATP + LYS + LTRNA -> AMP + PPI + LLTRNA	<u>6.1.1.6</u>
<b>5.9</b> Lysine degradation PATH:hsa00310		
<u>8424</u> BBOX, BBH, GAMMA-BBH, G-BBH		<u>1.14.11.1</u>
<u>5351</u> PLOD, LLH		<u>1.14.11.4</u>
<u>5352</u> PLOD2		<u>1.14.11.4</u>
<u>8985</u> PLOD3, LH3		<u>1.14.11.4</u>
<u>10157</u> LKR/SDH, AASS	LYS + NADPH + AKG -> NADP + H2O + SAC SAC + H2O + NAD -> GLU + NADH + AASA	<u>1.5.1.9</u>
<b>5.10</b> Arginine and proline metabolism PATH:hsa00330		
<u>5009</u> OTC	ORNm + CAPm -> CITRm + Pim + Hm	<u>2.1.3.3</u>
<u>383</u> ARG1	ARG -> ORN + UREA	<u>3.5.3.1</u>
<u>384</u> ARG2	ARG -> ORN + UREA	<u>3.5.3.1</u>
<u>4842</u> NOS1, NOS		<u>1.14.13.39</u>
<u>4843</u> NOS2A, NOS2		<u>1.14.13.39</u>
<u>4846</u> NOS3, ECNOS		<u>1.14.13.39</u>
<u>4942</u> OAT	ORN + AKG -> GLUGSAL + GLU	<u>2.6.1.13</u>

<u>5831</u> PYCR1, P5C, PYCR	P5C + NADPH $\rightarrow$ PRO + NADP P5C + NADH $\rightarrow$ PRO + NAD PHC + NADPH $\rightarrow$ HPRO + NADP PHC + NADH $\rightarrow$ HPRO + NAD	<u>1.5.1.2</u>
<u>5033</u> P4HA1, P4HA		<u>1.14.11.2</u>
<u>5917</u> RARS	ATP + ARG + ATRNA $\rightarrow$ AMP + PPI + ALTRNA	<u>6.1.1.19</u>
<u>1152</u> CKB, CKBB	PCRE + ADP $\rightarrow$ CRE + ATP	<u>2.7.3.2</u>
<u>1158</u> CKBE		<u>2.7.3.2</u>
<u>1158</u> CKM, CKMM		<u>2.7.3.2</u>
<u>1159</u> CKMT1, CKMT, UMTCK		<u>2.7.3.2</u>
<u>1160</u> CKMT2, SMTCK		<u>2.7.3.2</u>
<u>6723</u> SRM, SPS1, SRML1	PTRSC + SAM $\rightarrow$ SPRMD + 5MTA	<u>2.5.1.16</u>
<u>262</u> AMD1, ADOMETDC	SAM $\leftrightarrow$ DSAM + CO2	<u>4.1.1.50</u>
<u>263</u> AMDP1, AMD, AMD2	SAM $\leftrightarrow$ DSAM + CO2	<u>4.1.1.50</u>
<u>1725</u> DHPS	SPRMD + Qm $\rightarrow$ DAPRP + QH2m	<u>1.5.99.6</u>
<u>6611</u> SMS	DSAM + SPRMD $\rightarrow$ 5MTA + SPRM	<u>2.5.1.22</u>
<u>4953</u> ODC1	ORN $\rightarrow$ PTRSC + CO2	<u>4.1.1.17</u>
<u>6303</u> SAT, SSAT		<u>2.3.1.57</u>
<b>5.11 Histidine metabolism PATH:hsa00340</b>		
<u>10841</u> FTCD	FIGLU + THF $\rightarrow$ NFTHF + GLU	<u>2.1.2.5</u>
<u>3067</u> HDC		<u>4.3.1.4</u>
<u>1644</u> DDC, AADC		<u>4.1.1.22</u>
<u>3176</u> HNMT		<u>4.1.1.28</u>
<u>218</u> ALDH3	ACAL + NAD $\rightarrow$ NADH + AC	<u>2.1.1.8</u>
<u>220</u> ALDH6	ACAL + NAD $\rightarrow$ NADH + AC	<u>12.1.5</u>
<u>221</u> ALDH7, ALDH4	ACAL + NAD $\rightarrow$ NADH + AC	<u>12.1.5</u>
<u>222</u> ALDH8	ACAL + NAD $\rightarrow$ NADH + AC	<u>12.1.5</u>
<u>3035</u> HARS	ATP + HIS + HTRNA $\rightarrow$ AMP + PPI + HHTRNA	<u>6.1.1.21</u>
<b>5.12 Tyrosine metabolism PATH:hsa00350</b>		
<u>6898</u> TAT	AKG + TYR $\rightarrow$ HPHYR + GLU	<u>2.6.1.5</u>
<u>3242</u> HPD, PPD	HPHYR + O2 $\rightarrow$ HGTS + CO2	<u>1.13.11.27</u>
<u>3081</u> HGD, AKU, HGO	HGTS + O2 $\rightarrow$ MACA	<u>1.13.11.5</u>
<u>2954</u> GSTZ1, MAA1	MACA $\rightarrow$ FACA	<u>5.2.1.2</u>
<u>2184</u> FAH	FACA + H2O $\rightarrow$ FUM + ACA	<u>2.5.1.18</u>
<u>7299</u> TYR, OCAIA		<u>3.7.1.2</u>
<u>7054</u> TH, TYH		<u>1.14.18.1</u>
<u>1621</u> DBH		<u>1.14.16.2</u>
<u>5409</u> PNMT, PENT		<u>1.14.17.1</u>
<u>1312</u> COMT		<u>2.1.1.28</u>
<u>7173</u> TPO, TPX		<u>2.1.1.6</u>
<b>5.13 Phenylalanine metabolism PATH:hsa00360</b>		
<u>501</u> ATQ1		<u>1.2.1.-</u>
<b>5.14 Tryptophan metabolism PATH:hsa00380</b>		
<u>6999</u> TDO2, TPH2, TRPO, TDO	TRP + O2 $\rightarrow$ FKYN	<u>1.13.11.11</u>
<u>8564</u> KMO	KYN + NADPH + O2 $\rightarrow$ HKYN + NADP + H2O	<u>1.14.13.9</u>
<u>8942</u> KYNU	KYN $\rightarrow$ ALA + AN	<u>3.7.1.3</u>
<u>23498</u> HAAO, HAO, 3-HAO	HKYN + H2O $\rightarrow$ HAN + ALA	
<u>7166</u> TPH, TPRH	HAN + O2 $\rightarrow$ CMUSA	<u>1.13.11.6</u>
<u>438</u> ASMT, HIOMT, ASMTY		<u>1.14.16.4</u>
<u>15</u> AANAT, SNAT		<u>2.1.1.4</u>
<u>3620</u> INDO, IDO		<u>2.3.1.87</u>
<u>10352</u> WARS2	ATPm + TRPm + TRNAm $\rightarrow$ AMPm + PPIm + TRPTRNAm	<u>1.13.11.42</u>
<u>7453</u> WARS, IFP53, IFI53, GAMMA-2	ATP + TRP + TRNA $\rightarrow$ AMP + PPI + TRPTRNA	<u>6.1.1.2</u>
<u>4734</u> NEDD4, KIAA0093		<u>6.1.1.2</u>
<b>5.15 Phenylalanine, tyrosine and tryptophan biosynthesis PATH:hsa00400</b>		
<u>5053</u> PAH, PKU1	PHE + THBP + O2 $\rightarrow$ TYR + DHBP + H2O	<u>6.1.1.2</u>
<u>10667</u> FARS1		<u>6.1.1.20</u>
<u>2193</u> FARSL, CML33		<u>6.1.1.20</u>
<u>10056</u> PheHB		<u>6.1.1.20</u>
<u>8565</u> YARS, TYRRS, YTS, YRS		<u>6.1.1.1</u>
<b>5.16 Urea cycle and metabolism of amino groups PATH:hsa00220</b>		
<u>5832</u> PYCS	GLUP + NADH $\rightarrow$ NAD + Pi + GLUGSAL	<u>2.7.2.11</u>
	GLUP + NADPH $\rightarrow$ NADP + Pi + GLUGSAL	<u>1.2.1.41</u>

## 95 ACY1

3.5.1.14

## 6. Metabolism of Other Amino Acids

## 6.1 beta-Alanine metabolism PATH:hsa00410

## 6.2 Taurine and hypotaurine metabolism PATH:hsa00430

2678 GGT1, GTG, D22S672, D22S732, 2678 GGT	RGT + ALA → CGLY + ALAGLY	<u>2.3.2.2</u>
2679 GGT2, GGT	RGT + ALA → CGLY + ALAGLY	<u>2.3.2.2</u>
2680 GGT3	RGT + ALA → CGLY + ALAGLY	<u>2.3.2.2</u>
2687 GGT1A1, GGT-REL, DKFZP566O011	RGT + ALA → CGLY + ALAGLY	<u>2.3.2.2</u>

## 6.3 Aminophosphonate metabolism PATH:hsa00440

5130 PCYT1A, CTPCT, CT, PCYT1 9791 PTDSS1, KIAA0024, PSSA	PCHO + CTP → CDPCHO + PPI CDPDG + SER <> CMP + PS	<u>2.7.7.15</u> <u>2.7.8.-</u>
--	--	-----------------------------------

## 6.4 Selenoamino acid metabolism PATH:hsa00450

22928 SPS2 22929 SPS, SELD		<u>2.7.9.3</u> <u>2.7.9.3</u>
-------------------------------	--	----------------------------------

## 6.5 Cyanoamino acid metabolism PATH:hsa00460

## 6.6 D-Glutamine and D-glutamate metabolism PATH:hsa00471

## 6.7 D-Arginine and D-ornithine metabolism PATH:hsa00472

## 6.9 Glutathione metabolism PATH:hsa00480

5182 PEPB		<u>3.4.11.4</u>
2655 GCTG		<u>2.3.2.4</u>
2876 GPX1, GSHPX1	2 RGT + H2O2 <> OGT	<u>1.1.1.9</u>
2877 GPX2, GSHPX-GI	2 RGT + H2O2 <> OGT	<u>1.1.1.9</u>
2878 GPX3	2 RGT + H2O2 <> OGT	<u>1.1.1.9</u>
2879 GPX4	2 RGT + H2O2 <> OGT	<u>1.1.1.9</u>
2880 GPX5	2 RGT + H2O2 <> OGT	<u>1.1.1.9</u>
2881 GPX6	2 RGT + H2O2 <> OGT	<u>1.1.1.9</u>
2938 GSTA1		<u>2.5.1.18</u>
2939 GSTA2, GST2		<u>2.5.1.18</u>
2940 GSTA3		<u>2.5.1.18</u>
2941 GSTA4		<u>2.5.1.18</u>
2944 GSTM1, GST1, MU		<u>2.5.1.18</u>
2946 GSTM2, GST4		<u>2.5.1.18</u>
2947 GSTM3, GST5		<u>2.5.1.18</u>
2948 GSTM4		<u>2.5.1.18</u>
2949 GSTM5		<u>2.5.1.18</u>
2950 GSTP1, FAEES3, DFN7, GST3, PI		<u>2.5.1.18</u>
2952 GSTT1		<u>2.5.1.18</u>
2953 GSTT2		<u>2.5.1.18</u>
4257 MGST1, GST12, MGST, MGST-I		<u>2.5.1.18</u>
4258 MGST2, GST2, MGST-II		<u>2.5.1.18</u>
4259 MGST3, GST-III		<u>2.5.1.18</u>

## 7. Metabolism of Complex Carbohydrates

## 7.1 Starch and sucrose metabolism PATH:hsa00500

6476 SI		<u>3.2.1.10</u> <u>3.2.1.48</u>
11181 TREH, TRE, TREA	TRE → 2 GLC	<u>3.2.1.28</u>
2990 GUSB		<u>3.2.1.31</u>
2632 GBE1	GLYCOGEN + PI → G1P	<u>2.4.1.18</u>
5834 PYGB	GLYCOGEN + PI → G1P	<u>2.4.1.1</u>
5836 PYGL	GLYCOGEN + PI → G1P	<u>2.4.1.1</u>
5837 PYGM	GLYCOGEN + PI → G1P	<u>2.4.1.1</u>
2997 GYS1, GYS	UDPG → UDP + GLYCOGEN	<u>2.4.1.11</u>
2998 GYS2	UDPG → UDP + GLYCOGEN	<u>2.4.1.11</u>
276 AMY1A, AMY1		<u>3.2.1.1</u>
277 AMY1B, AMY1		<u>3.2.1.1</u>
278 AMY1C, AMY1		<u>3.2.1.1</u>
279 AMY2A, AMY2		<u>3.2.1.1</u>
280 AMY2B, AMY2		<u>3.2.1.1</u>
178 AGL, GDE		<u>2.4.1.25</u> <u>3.2.1.33</u>
10000 AKT3, PKBG, RAC-GAMMA, PRKBG		<u>2.7.1.-</u>
1017 CDK2		<u>2.7.1.-</u>
1018 CDK3		<u>2.7.1.-</u>
1019 CDK4, PSK-J3		<u>2.7.1.-</u>
1020 CDK5, PSSALRE		<u>2.7.1.-</u>

<u>1021</u> CDK6, PLSTIRE	2.7.1-
<u>1022</u> CDK7, CAK1, STK1, CDKN7	2.7.1-
<u>1024</u> CDK8, K35	2.7.1-
<u>1025</u> CDK9, PITALRE, CDC2L4	2.7.1-
<u>1028</u> PAK4	2.7.1-
<u>10746</u> MAP3K2, MEKK2	2.7.1-
<u>1111</u> CHEK1, CHK1	2.7.1-
<u>11200</u> RAD53, CHK2, CDS1, HUCDS1	2.7.1-
<u>1195</u> CLK1, CLK	2.7.1-
<u>1326</u> MAP3K8, COT, EST, ESTF, TPL-2	2.7.1-
<u>1432</u> MAPK14, CSBP2, CSPB1, PRKM14, PRKM15, CSBP1, P38, MX12	2.7.1-
<u>1452</u> CSNK1A1	2.7.1-
<u>1453</u> CSNK1D, HCKID	2.7.1-
<u>1454</u> CSNK1E, HCKIE	2.7.1-
<u>1455</u> CSNK1G2	2.7.1-
<u>1456</u> CSNK1G3	2.7.1-
<u>1612</u> DAPK1, DAPK	2.7.1-
<u>1760</u> DMPK, DM, DMK, DM1	2.7.1-
<u>1859</u> DYRK1A, DYRK1, DYRK, MNB, MNBH	2.7.1-
<u>208</u> AKT2, RAC-BETA, PRKBB, PKBBETA	2.7.1-
<u>269</u> AMHR2, AMHR	2.7.1-
<u>27330</u> RPS6KA6, RSK4	2.7.1-
<u>2868</u> GPRK2L, GPRK4	2.7.1-
<u>2869</u> GPRK5, GRK5	2.7.1-
<u>2870</u> GPRK6, GRK6	2.7.1-
<u>29904</u> HSU93850	2.7.1-
<u>30811</u> HUNK	2.7.1-
<u>3611</u> ILK, P59	2.7.1-
<u>3654</u> IRAK1, IRAK	2.7.1-
<u>369</u> ARAF1, PKS2, RAF1A	2.7.1-
<u>370</u> ARAF2P, PKS1, ARAF2	2.7.1-
<u>3984</u> LIMK1, LIMK	2.7.1-
<u>3985</u> LIMK2	2.7.1-
<u>4117</u> MAK	2.7.1-
<u>4140</u> MARK3, KP78	2.7.1-
<u>4215</u> MAP3K3, MAPKKK3, MEKK3	2.7.1-
<u>4216</u> MAP3K4, MAPKKK4, MTK1, MEKK4, KIAA0213	2.7.1-
<u>4217</u> MAP3K5, ASK1, MAPKKK5, MEKK5	2.7.1-
<u>4293</u> MAP3K9, PRKE1, MLK1	2.7.1-
<u>4294</u> MAP3K10, MLK2, MST	2.7.1-
<u>4342</u> MOS	2.7.1-
<u>4751</u> NEK2, NLK1	2.7.1-
<u>4752</u> NEK3	2.7.1-
<u>5058</u> PAK1, PAKalpha	2.7.1-
<u>5062</u> PAK2, PAK65, PAKgamma	2.7.1-
<u>5063</u> PAK3, MRX30, PAK3beta	2.7.1-
<u>5127</u> PCTK1, PCTGAIRE	2.7.1-
<u>5128</u> PCTK2	2.7.1-
<u>5129</u> PCTK3, PCTAIRE	2.7.1-
<u>5292</u> PIM1, PIM	2.7.1-
<u>5347</u> PLK, PLK1	2.7.1-
<u>5562</u> PRKAA1	2.7.1-
<u>5563</u> PRKAA2, AMPK, PRKAA	2.7.1-
<u>5578</u> PRKCA, PKCA	2.7.1-
<u>5579</u> PRKCB1, PKCB, PRKCB, PRKCB2	2.7.1-
<u>5580</u> PRKCD	2.7.1-
<u>5581</u> PRKCE	2.7.1-
<u>5582</u> PRKCG, PKCC, PKCG	2.7.1-
<u>5583</u> PRKCH, PKC-L, PRKCL	2.7.1-
<u>5584</u> PRKCI, DKS1179E, PKCI	2.7.1-
<u>5585</u> PRKCL1, PAK1, PRK1, DBK, PKN	2.7.1-
<u>5586</u> PRKCL2, PRK2	2.7.1-
<u>5588</u> PRKCQ	2.7.1-

<u>5590</u> PRKCZ	<u>2.7.1-</u>
MAPK1, PRKM1, P41MAPK,	
<u>5594</u> P42MAPK, ERK2, ERK, MAPK2,	<u>2.7.1-</u>
PRKM2	
<u>5595</u> MAPK3, ERK1, PRKM3, P44ERK1,	<u>2.7.1-</u>
P44MAPK	
<u>5597</u> MAPK6, PRKM6, P97MAPK, ERK3	<u>2.7.1-</u>
<u>5598</u> MAPK7, BMK1, ERK5, PRKM7	<u>2.7.1-</u>
MAPK8, JNK, JNK1, SAPK1, PRKM8,	
<u>5599</u> JNK1A2	<u>2.7.1-</u>
MAPK9, JNK2, PRKM9, P54ASAPK,	
<u>5601</u> JUNKINASE	<u>2.7.1-</u>
MAPK10, JNK3, PRKM10, P493F12,	
<u>5602</u> P54BSAPK	<u>2.7.1-</u>
MAPK13, SAPK4, PRKM13,	
<u>5603</u> P38DELTA	<u>2.7.1-</u>
MAP2K1, MAPKK1, MEK1, MKK1,	
<u>5604</u> PRKMK1	<u>2.7.1-</u>
MAP2K2, MEK2, PRKMK2	
<u>5605</u> MAP2K3, MEK3, MKK3, PRKMK3	<u>2.7.1-</u>
MAP2K5, MEK5, PRKMK5	
MAP2K6, MEK6, MKK6, SAPKK3,	
<u>5608</u> PRKMK6	<u>2.7.1-</u>
MAP2K7, MAPKK7, MKK7, PRKMK7,	
<u>5609</u> JNKK2	<u>2.7.1-</u>
PRKR, EIF2AK1, PKR	
<u>5610</u> PRKX, PKX1	<u>2.7.1-</u>
<u>5613</u> RAF1	<u>2.7.1-</u>
BCR, CML, PHL, BCR1, D22S11,	
<u>613</u> D22S662	<u>2.7.1-</u>
RPS6KA1, HU-1, RSK, RSK1,	
<u>6195</u> MAPKAPK1A	<u>2.7.1-</u>
RPS6KA2, HU-2, MAPKAPK1C, RSK,	
<u>6196</u> RSK3	<u>2.7.1-</u>
RPS6KA3, RSK2, HU-2, HU-3, RSK,	
<u>6197</u> MAPKAPK1B, ISPK-1	<u>2.7.1-</u>
6198 RPS6KB1, STK14A	
<u>6199</u> RPS6KB2, P70-BETA, P70S6KB	<u>2.7.1-</u>
MAPK12, ERK6, PRKM12, SAPK3,	
<u>6300</u> P38GAMMA, SAPK-3	<u>2.7.1-</u>
MAP2K4, JNKK1, MEK4, PRKMK4,	
<u>6416</u> SERK1, MKK4	<u>2.7.1-</u>
<u>6446</u> SGK	<u>2.7.1-</u>
<u>658</u> BMPR1B, ALK-6, ALK6	<u>2.7.1-</u>
<u>659</u> BMPR2, BMPR-II, BMPR3, BRK-3	<u>2.7.1-</u>
<u>673</u> BRAF	<u>2.7.1-</u>
<u>6792</u> STK9	<u>2.7.1-</u>
<u>6794</u> STK11, LKB1, PJS	<u>2.7.1-</u>
<u>6885</u> MAP3K7, TAK1	<u>2.7.1-</u>
<u>699</u> BUB1	<u>2.7.1-</u>
<u>701</u> BUB1B, BUBR1, MAD3L	<u>2.7.1-</u>
<u>7016</u> TESK1	<u>2.7.1-</u>
<u>7272</u> TTK, MPS1L1	<u>2.7.1-</u>
<u>7867</u> MAPKAPK3, 3PK, MAPKAP3	<u>2.7.1-</u>
<u>8408</u> ULK1	<u>2.7.1-</u>
<u>8558</u> CDK10, PISSLRE	<u>2.7.1-</u>
<u>8621</u> CDC2L5, CDC2L, CHED	<u>2.7.1-</u>
<u>8737</u> RIPK1, RIP	<u>2.7.1-</u>
<u>8814</u> CDKL1, KKLALRE	<u>2.7.1-</u>
<u>8899</u> PRP4, PR4H	<u>2.7.1-</u>
<u>9064</u> MAP3K6, MAPKKK6	<u>2.7.1-</u>
<u>9149</u> DYRK1B	<u>2.7.1-</u>
<u>92</u> ACVR2, ACTRII	<u>2.7.1-</u>
<u>9201</u> DCAMKL1, KIAA0369	<u>2.7.1-</u>
<u>93</u> ACVR2B	<u>2.7.1-</u>
<u>983</u> CDC2	<u>2.7.1-</u>
<u>984</u> CDC2L1	<u>2.7.1-</u>

<u>5205</u> FIC1, BRIC, PFIC1, PFIC, ATP8B1		<u>3.6.1-</u>
	DHPP $\rightarrow$ DHP + PI	
	GTP $\rightarrow$ GSN + 3 PI	
	DGTP $\rightarrow$ DG + 3 PI	
<b>7.2</b> Glycoprotein biosynthesis PATH:hsa00510		<b>2.7.8.15</b>
<u>1798</u> DPAGT1, DPAGT, UGAT, UAGT, <u>D11S366</u> , DGPT, DPAGT2, GPT		<u>2.4.1.117</u>
<u>29880</u> ALG5		<u>2.4.1.83</u>
<u>8813</u> DPM1	GDPMAN + DOLP $\rightarrow$ GDP + DOLMANP	<u>2.4.1.119</u>
<u>1650</u> DDOST, OST, OST48, KIAA0115		<u>2.4.1.119</u>
<u>6184</u> RPN1		<u>2.4.1.119</u>
<u>6185</u> RPN2		<u>5.3.4.1</u>
<u>10130</u> P5		<u>5.3.4.1</u>
<u>10954</u> PDIR		<u>5.3.4.1</u>
<u>11008</u> PDI		<u>5.3.4.1</u>
GRP58, ERp57, ERp60, ERp61, <u>2923</u> GRP57, P58, PI-PLC, ERP57, ERP60, ERP61		<u>5.3.4.1</u>
<u>5034</u> P4HB, PROHB, PO4DB, ERBA2L		<u>3.2.1.106</u>
<u>7841</u> GCS1		<u>3.2.1.113</u>
<u>4121</u> MAN1A1, MAN9, HUMM9		<u>2.4.1.101</u>
<u>4245</u> MGAT1, GLYT1, GLCNAC-TI, GNT-I, MGAT		<u>3.2.1.114</u>
<u>4122</u> MAN2A2, MANA2X		<u>3.2.1.114</u>
<u>4124</u> MAN2A1, MANA2		<u>2.4.1.143</u>
MGAT2, CDGS2, GNT-II, GLCNACTII, <u>4247</u> GNT2		<u>2.4.1.144</u>
<u>4248</u> MGAT3, GNT-III		<u>2.4.99.6</u>
<u>6487</u> SIAT6, ST3GALII		<u>2.4.99.1</u>
<u>6480</u> SIAT1		<u>2.5.1-</u>
<u>2339</u> FNTA, FPTA, PGGT1A		<u>2.5.1-</u>
<u>2342</u> FNTB, FPTB		<u>2.5.1-</u>
<u>5229</u> PGGT1B, BGG1, GGT1		<u>2.5.1-</u>
<u>5875</u> RABGGTA		<u>2.5.1-</u>
<u>5876</u> RABGGTB		<u>2.5.1-</u>
<u>1352</u> COX10		<u>2.5.1-</u>
<b>7.3</b> Glycoprotein degradation PATH:hsa00511		<u>3.2.1.18</u>
<u>4758</u> NEU1, NEU		<u>3.2.1.52</u>
<u>3073</u> HEXA, TSD		<u>3.2.1.52</u>
<u>3074</u> HEXB		<u>3.2.1.24</u>
<u>4123</u> MAN2C1, MANA, MANA1, MAN6A8		<u>3.2.1.24</u>
<u>4125</u> MAN2B1, MANB, LAMAN		<u>3.2.1.25</u>
<u>4126</u> MANBA, MANB1		<u>3.2.1.51</u>
<u>2517</u> FUCA1		<u>3.2.1.51</u>
<u>2519</u> FUCA2		<u>3.5.1.26</u>
<u>175</u> AGA, AGU		
<b>7.4</b> Aminosugars metabolism PATH:hsa00530	UTP + NAGA1P $\leftrightarrow$ UDPNAG + PPI	<u>2.7.7.23</u>
<u>6675</u> UAP1, SPAG2, AGX1		<u>5.1.3.14</u>
<u>10020</u> GNE, GLCNE		<u>2.7.7.43</u>
<u>22951</u> CMAS		<u>1.6.2.2</u>
<u>1727</u> DIA1		<u>3.2.1.50</u>
<u>4669</u> NAGLU, NAG		
<b>7.5</b> Lipopolysaccharide biosynthesis PATH:hsa00540		<u>2.4.99.-</u>
<u>6485</u> SIAT5, SAT3, STZ		<u>2.4.99.-</u>
<u>7903</u> SIAT8D, PST, PST1, ST8SIA-IV		<u>2.4.99.-</u>
<u>8128</u> SIAT8B, STX, ST8SIA-II		
<b>7.7</b> Glycosaminoglycan degradation PATH:hsa00531		<u>3.1.6.13</u>
<u>3423</u> IDS, MPS2, SIDS		<u>3.2.1.76</u>
<u>3425</u> IDUA, IDA		<u>3.1.6.12</u>
<u>411</u> ARSB		<u>3.1.6.14</u>
<u>2799</u> GNS, G6S		<u>3.1.6.14</u>
<u>2588</u> GALNS, MPS4A, GALNAC6S, GAS		<u>3.1.6.4</u>
<b>8.</b> Metabolism of Complex Lipids		
<b>8.1</b> Glycerolipid metabolism PATH:hsa00561		
<u>10554</u> AGPAT1, LPAAT-ALPHA, G15	AGL3P + 0.017 C100ACP + 0.052 C120ACP + 0.100 C140ACP + 0.270 C160ACP + 0.169 C161ACP + 0.055 C180ACP + 0.235 C181ACP + 0.093 C182ACP $\rightarrow$ PA + ACP	<u>2.3.1.51</u>

<u>10555</u> AGPAT2, LPAAT-BETA	AGL3P + 0.017 C100ACP + 0.062 C120ACP + 0.100 C140ACP + 0.270 C160ACP + 0.169 C161ACP + 0.055 C180ACP + 0.235 C181ACP + 0.093 C182ACP $\rightarrow$ PA + ACP	<u>2.3.1.51</u>
<u>1606</u> DGKA, DAGK, DAGK1		<u>2.7.1.107</u>
<u>1608</u> DGKG, DAGK3		<u>2.7.1.107</u>
<u>1609</u> DGKQ, DAGK4		<u>2.7.1.107</u>
<u>8525</u> DGKZ, DAGK5, HDGKZETA		<u>2.7.1.107</u>
<u>8526</u> DGKE, DAGK6, DGK		<u>2.7.1.107</u>
<u>8527</u> DGKD, DGKDELTA, KIAA0145		<u>2.7.1.107</u>
<u>1120</u> CHKL	ATP + CHO $\rightarrow$ ADP + PCHO	<u>2.7.1.32</u>
EK1	ATP + ETHM $\rightarrow$ ADP + PETHM	<u>2.7.1.82</u>
<u>1119</u> CHK, CK1	ATP + CHO $\rightarrow$ ADP + PCHO	<u>2.7.1.32</u>
43 ACHE, YT		<u>3.1.1.7</u>
<u>1103</u> CHAT		<u>2.3.1.6</u>
<u>5337</u> PLD1		<u>3.1.4.4</u>
<u>26279</u> PLA2G2D, SPLA2S		<u>3.1.1.4</u>
<u>30814</u> PLA2G2E		<u>3.1.1.4</u>
<u>5319</u> PLA2G1B, PLA2, PLA2A, PPLA2		<u>3.1.1.4</u>
<u>5320</u> PLA2G2A, MOM1, PLA2B, PLA2L		<u>3.1.1.4</u>
<u>5322</u> PLA2G5		<u>3.1.1.4</u>
<u>8398</u> PLA2G6, IPLA2		<u>3.1.1.4</u>
<u>8399</u> PLA2G10, SPLA2		<u>3.1.1.4</u>
<u>1040</u> CDS1	PA + CTP $\leftrightarrow$ CDPDG + PPI	<u>2.7.7.41</u>
<u>10423</u> PIS	CDPDG + MYO1 $\rightarrow$ CMP + PINS	<u>2.7.8.11</u>
<u>2710</u> GK	GL + ATP $\rightarrow$ GL3P + ADP	<u>2.7.1.30</u>
<u>2820</u> GPD2	GL3Pm + FADm $\rightarrow$ T3P2m + FADH2m	<u>1.1.99.5</u>
<u>2819</u> GPD1	T3P2 + NADH $\leftrightarrow$ GL3P + NAD	<u>1.1.1.8</u>
248 ALPI	AHTD $\rightarrow$ DHP + 3 PI	<u>3.1.3.1</u>
249 ALPL, HOPS, TNSALP	AHTD $\rightarrow$ DHP + 3 PI	<u>3.1.3.1</u>
250 ALPP	AHTD $\rightarrow$ DHP + 3 PI	<u>3.1.3.1</u>
251 ALPPL2	AHTD $\rightarrow$ DHP + 3 PI	<u>3.1.3.1</u>
439 ASNA1, ARSA-1		<u>3.6.1.16</u>
<u>8694</u> DGAT, ARGP1	DAGLY + 0.017 C100ACP + 0.062 C120ACP + 0.100 C140ACP + 0.270 C160ACP + 0.169 C161ACP + 0.055 C180ACP + 0.235 C181ACP + 0.093 C182ACP $\rightarrow$ TAGLY + ACP	<u>2.3.1.20</u>
<u>3989</u> LIPB		<u>3.1.1.3</u>
<u>3990</u> LIPC, HL		<u>3.1.1.3</u>
<u>5406</u> PNLLIP		<u>3.1.1.3</u>
<u>5407</u> PNLLPRP1, PLRP1		<u>3.1.1.3</u>
<u>5408</u> PNLLPRP2, PLRP2		<u>3.1.1.3</u>
<u>8513</u> LIPF, HGL, HLAL		<u>3.1.1.3</u>
<u>4023</u> LPL, LIPD		<u>3.1.1.34</u>
<u>8443</u> GNPAT, DHAPAT, DAP-AT		<u>2.3.1.42</u>
AGPS, ADAP-S-, ADAS, ADHAPS,		
<u>8540</u> ADPS, ALDHPSY		<u>2.5.1.26</u>
<u>4186</u> MDCR, MDS, LIS1		<u>3.1.1.47</u>
<u>5048</u> PAFAH1B1, LIS1, MDCR, PAFAH		<u>3.1.1.47</u>
<u>5049</u> PAFAH1B2		<u>3.1.1.47</u>
<u>5050</u> PAFAH1B3		<u>3.1.1.47</u>
<u>5051</u> PAFAH2, HSD-PLA2		<u>3.1.1.47</u>
<u>7941</u> PLA2G7, PAFAH, LDL-PLA2		<u>3.1.1.47</u>
8.2 Inositol phosphate metabolism PATH:hsa00562		
<u>5290</u> PIK3CA	ATP + PINS $\rightarrow$ ADP + PINSP	<u>2.7.1.137</u>
<u>5291</u> PIK3CB, PIK3C1	ATP + PINS $\rightarrow$ ADP + PINSP	<u>2.7.1.137</u>
<u>5293</u> PIK3CD	ATP + PINS $\rightarrow$ ADP + PINSP	<u>2.7.1.137</u>
<u>5294</u> PIK3CG	ATP + PINS $\rightarrow$ ADP + PINSP	<u>2.7.1.137</u>
<u>5297</u> PIK4CA, PI4K-ALPHA	ATP + PINS $\rightarrow$ ADP + PINSP4P	<u>2.7.1.67</u>
<u>5305</u> PIP5K2A	PINS4P + ATP $\rightarrow$ D45PI + ADP	<u>2.7.1.68</u>
<u>5330</u> PLCB2	D45PI $\rightarrow$ TPI + DAGLY	<u>3.1.4.11</u>
<u>5331</u> PLCB3	D45PI $\rightarrow$ TPI + DAGLY	<u>3.1.4.11</u>
<u>5333</u> PLCD1	D45PI $\rightarrow$ TPI + DAGLY	<u>3.1.4.11</u>
<u>5335</u> PLCG1, PLC1	D45PI $\rightarrow$ TPI + DAGLY	<u>3.1.4.11</u>
<u>5336</u> PLCG2	D45PI $\rightarrow$ TPI + DAGLY	<u>3.1.4.11</u>
<u>3612</u> IMPA1, IMPA	MI1P $\rightarrow$ MYO1 + PI	<u>3.1.3.25</u>
<u>3613</u> IMPA2	MI1P $\rightarrow$ MYO1 + PI	<u>3.1.3.25</u>
<u>3628</u> INPP1		<u>3.1.3.57</u>

<u>3632</u> INPP5A		<u>3.1.3.56</u>
<u>3633</u> INPP5B		<u>3.1.3.56</u>
<u>3636</u> INPPL1, SHIP2		<u>3.1.3.56</u>
<u>4952</u> OCRL, LOCRL, OCRL1, INPP5F		<u>3.1.3.56</u>
<u>8867</u> SYNJ1, INPP5G		<u>3.1.3.56</u>
<u>3706</u> ITPKA		<u>2.7.1.127</u>
<u>51477</u> ISYNA1	G6P $\rightarrow$ MI1P	<u>5.5.1.4</u>
<u>3631</u> INPP4A, INPP4		<u>3.1.3.66</u>
<u>8821</u> INPP4B		<u>3.1.3.66</u>
<b>8.3</b> Sphingophospholipid biosynthesis PATH:hsa00570		<u>3.1.4.12</u>
<u>6609</u> SMPD1, NPD		
<b>8.4</b> Phospholipid degradation PATH:hsa00580		<u>3.1.1.5</u>
<u>1178</u> CLC		<u>3.1.1.5</u>
<u>5321</u> PLA2G4A, CPLA2-ALPHA, PLA2G4		
<b>8.5</b> Sphingoglycolipid metabolism PATH:hsa00600		
<u>10558</u> SPTLC1, LCB1, SPTI	PALCOA + SER $\rightarrow$ COA + DHSPH + CO2	<u>2.3.1.50</u>
<u>9517</u> SPTLC2, KIAA0526, LCB2	PALCOA + SER $\rightarrow$ COA + DHSPH + CO2	<u>2.3.1.50</u>
<u>427</u> ASAHL, AC, PHP32		<u>3.5.1.23</u>
<u>7357</u> UGCG, GCS		<u>2.4.1.80</u>
<u>2629</u> GBA, GLUC		<u>3.2.1.45</u>
<u>2583</u> GALGT, GALNACT		<u>2.4.1.92</u>
<u>6489</u> SIAT8A, SIAT8, ST8SIA-I		<u>2.4.99.8</u>
<u>6481</u> SIAT2		<u>2.4.99.2</u>
<u>4668</u> NAGA, D22S674, GALB		<u>3.2.1.49</u>
<u>9514</u> CST		<u>2.8.2.11</u>
<u>410</u> ARSA, MLD		<u>3.1.6.8</u>
<b>8.6</b> Blood group glycolipid biosynthesis - lact series PATH:hsa00601		<u>2.4.1.40</u>
<u>28</u> ABO		<u>2.4.1.37</u>
<u>2525</u> FUT3, LE		<u>2.4.1.65</u>
<u>2527</u> FUT5, FUC-TV		<u>2.4.1.65</u>
<u>2528</u> FUT6		<u>2.4.1.65</u>
<u>2523</u> FUT1, H, HH		<u>2.4.1.69</u>
<u>2524</u> FUT2, SE		<u>2.4.1.69</u>
<b>8.7</b> Blood group glycolipid biosynthesis - neolact series PATH:hsa00602		<u>2.4.1.150</u>
<u>2651</u> GCNT2, IGNT, NACGT1, NAGCT1		
<b>8.8</b> Prostaglandin and leukotriene metabolism PATH:hsa00590		
<u>239</u> ALOX12, LOG12		<u>1.13.11.31</u>
<u>246</u> ALOX15		<u>1.13.11.33</u>
<u>249</u> ALOX5		<u>1.13.11.34</u>
<u>4056</u> LTC4S		<u>2.5.1.37</u>
<u>4048</u> LTA4H		<u>3.3.2.6</u>
<u>4051</u> CYP4F3, CYP4F, LTB4H		<u>1.14.13.30</u>
<u>8529</u> CYP4F2		<u>1.14.13.30</u>
<u>5742</u> PTGS1, PGHS-1		<u>1.14.99.1</u>
<u>5743</u> PTGS2, COX-2, COX2		<u>1.14.99.1</u>
<u>27306</u> PGDS		<u>5.3.99.2</u>
<u>5730</u> PTGDS		<u>5.3.99.2</u>
<u>5740</u> PTGIS, CYP8, PGIS		<u>5.3.99.4</u>
<u>6916</u> TBXAS1, CYP5		<u>5.3.99.5</u>
<u>873</u> CBR1, CBR		<u>1.1.1.184</u>
<u>874</u> CBR3		<u>1.1.1.189</u>
<u>9. Metabolism of Cofactors and Vitamins</u>		
<b>9.2</b> Riboflavin metabolism PATH:hsa00740		
<u>52</u> ACP1	FMN $\rightarrow$ RIBOFLAV + PI	<u>3.1.3.48</u>
<u>53</u> ACP2	FMN $\rightarrow$ RIBOFLAV + PI	<u>3.1.3.2</u>
<u>54</u> ACP5, TRAP	FMN $\rightarrow$ RIBOFLAV + PI	<u>3.1.3.2</u>
<u>55</u> ACPP, PAP	FMN $\rightarrow$ RIBOFLAV + PI	<u>3.1.3.2</u>
<b>9.3</b> Vitamin B6 metabolism PATH:hsa00750		<u>2.7.1.35</u>
<u>8566</u> PDXK, PKH, PNK	PYRDX + ATP $\rightarrow$ P5P + ADP PDLA + ATP $\rightarrow$ PDLASP + ADP PL + ATP $\rightarrow$ PL5P + ADP	
<b>9.4</b> Nicotinate and nicotinamide metabolism PATH:hsa00760	QA + PRPP $\rightarrow$ NAMN + CO2 + PPI	<u>2.4.2.19</u>
<u>23475</u> QPRT		

<u>4837</u> NNMT		<u>2.1.1.1</u>
<u>683</u> BST1, CD157	NAD $\rightarrow$ NAM + ADPRIB	<u>3.2.2.5</u>
<u>952</u> CD38	NAD $\rightarrow$ NAM + ADPRIB	<u>3.2.2.5</u>
<u>23530</u> NNT		<u>1.6.1.2</u>
9.5 Pantothenate and CoA biosynthesis PATH:hsa00770		
9.6 Biotin metabolism PATH:hsa00780		
<u>3141</u> HLCs, HCS		<u>6.3.4.-</u>
		<u>6.3.4.9</u>
		<u>6.3.4.10</u>
		<u>6.3.4.11</u>
		<u>6.3.4.15</u>
		<u>3.5.1.12</u>
<u>686</u> BTD		
9.7 Folate biosynthesis PATH:hsa00790		
<u>2643</u> GCH1, DYT5, GCH, GTPCH1	GTP $\rightarrow$ FOR + AHTD	<u>3.5.4.16</u>
<u>1719</u> DHFR	DHF + NADPH $\rightarrow$ NADP + THF	<u>1.5.1.3</u>
<u>2356</u> FPGS	THF + ATP + GLU $\leftrightarrow$ ADP + PI + THFG	<u>6.3.2.17</u>
<u>8836</u> GGH, GH		<u>3.4.19.9</u>
<u>5805</u> PTS		<u>4.6.1.10</u>
<u>6697</u> SPR		<u>1.1.1.153</u>
<u>5860</u> QDPR, DHPR, PKU2	NADPH + DHBP $\rightarrow$ NADP + THBP	<u>1.6.9.7</u>
9.8 One carbon pool by folate PATH:hsa00670		
<u>10840</u> FTHFD		<u>1.5.1.6</u>
<u>10588</u> MTHFS	ATP + FTHF $\rightarrow$ ADP + PI + MTHF	<u>6.3.3.2</u>
9.10 Porphyrin and chlorophyll metabolism PATH:hsa00860		
<u>210</u> ALAD	2 ALAV $\rightarrow$ PBG	<u>4.2.1.24</u>
<u>3145</u> HMBS, PBGD, UPS	4 PBG $\rightarrow$ HMB + 4 NH3	<u>4.3.1.8</u>
<u>7390</u> UROS	HMB $\rightarrow$ UPRG	<u>4.2.1.75</u>
<u>7389</u> UROD	UPRG $\rightarrow$ 4 CO2 + CPP	<u>4.1.1.37</u>
<u>1371</u> CPO, CPX	O2 + CPP $\rightarrow$ 2 CO2 + PPHG	<u>1.3.3.3</u>
<u>5498</u> PPOX, PPO	O2 + PPHGm $\rightarrow$ PPIXm	<u>1.3.3.4</u>
<u>2235</u> FECH, FCE	PPIXm $\rightarrow$ PTHm	<u>4.99.1.1</u>
<u>3162</u> HMOX1, HO-1		<u>1.14.99.3</u>
<u>3163</u> HMOX2, HO-2		<u>1.14.99.3</u>
<u>644</u> BLVRA, BLVR		<u>1.3.1.24</u>
<u>645</u> BLVRB, FLR		<u>1.3.1.24</u>
		<u>1.6.9.1</u>
<u>2232</u> FDXR, ADXR		<u>1.18.1.2</u>
<u>3052</u> HCCS, CCHL		<u>4.4.1.17</u>
<u>1356</u> CP		<u>1.16.3.1</u>
9.11 Ubiquinone biosynthesis PATH:hsa00130		
<u>4938</u> OAS1, IFI-4, OIAS		<u>2.7.7.-</u>
<u>4939</u> OAS2, P69		<u>2.7.7.-</u>
<u>5557</u> PRIM1		<u>2.7.7.-</u>
<u>5558</u> PRIM2A, PRIM2		<u>2.7.7.-</u>
<u>5559</u> PRIM2B, PRIM2		<u>2.7.7.-</u>
<u>7015</u> TERT, EST2, TCS1, TP2, TRT		<u>2.7.7.-</u>
<u>8638</u> OASL, TRIP14		<u>2.7.7.-</u>
10. Metabolism of Other Substances		
10.1 Terpenoid biosynthesis PATH:hsa00900		
10.2 Flavonoids, stilbene and lignin biosynthesis PATH:hsa00940		
10.3 Alkaloid biosynthesis I PATH:hsa00950		
10.4 Alkaloid biosynthesis II PATH:hsa00950		
10.6 Streptomycin biosynthesis PATH:hsa00521		
10.7 Erythromycin biosynthesis PATH:hsa00522		
10.8 Tetracycline biosynthesis PATH:hsa00253		
10.14 gamma-Hexachlorocyclohexane degradation PATH:hsa00361		
<u>5444</u> PON1, ESA, PON		<u>3.1.8.1</u>
		<u>3.1.1.2</u>
<u>5445</u> PON2		<u>3.1.1.2</u>
		<u>3.1.8.1</u>
10.18 1,2-Dichloroethane degradation PATH:hsa00631		
10.20 Tetrachloroethene degradation PATH:hsa00625		
<u>2052</u> EPHX1, EPHX, MEH		<u>3.3.2.3</u>
<u>2053</u> EPHX2		<u>3.3.2.3</u>
10.21 Styrene degradation PATH:hsa00643		
11. Transcription (condensed)		
11.1 RNA polymerase PATH:hsa03020		

11.2 Transcription factors PATH:hsa03022		
12. Translation (condensed)		
12.1 Ribosome PATH:hsa03010		
12.2 Translation factors PATH:hsa03012		
1915 EEF1A1, EF1A, ALPHA, EEF-1,	<u>3.6.148</u>	
1916 EEF1A	<u>3.6.148</u>	
1917 EEF1A2, EF1A	<u>3.6.148</u>	
1938 EEF2, EF2, EEF-2	<u>3.6.148</u>	
12.3 Aminoacyl-tRNA biosynthesis PATH:hsa00970		
13. Sorting and Degradation (condensed)		
13.1 Protein export PATH:hsa03060		<u>3.4.21.89</u>
23478 SPC18		
13.4 Proteasome PATH:hsa03050		<u>3.4.99.46</u>
5687 PSMA6, IOTA, PROS27	<u>3.4.99.46</u>	
5683 PSMA2, HC3, MU, PMSA2, PSC2	<u>3.4.99.46</u>	
5685 PSMA4, HC9	<u>3.4.99.46</u>	
5688 PSMA7, XAPC7	<u>3.4.99.46</u>	
5686 PSMA5, ZETA, PSC5	<u>3.4.99.46</u>	
5682 PSMA1, HC2, NU, PROS30	<u>3.4.99.46</u>	
5684 PSMA3, HC8	<u>3.4.99.46</u>	
5698 PSMB9, LMP2, RING12	<u>3.4.99.46</u>	
5695 PSMB7, Z	<u>3.4.99.46</u>	
5691 PSMB3, HC10-II	<u>3.4.99.46</u>	
5690 PSMB2, HC7-I	<u>3.4.99.46</u>	
5693 PSMB5, LMPX, MB1	<u>3.4.99.46</u>	
5689 PSMB1, HC5, PMSB1	<u>3.4.99.46</u>	
5692 PSMB4, HN3, PRDS26	<u>3.4.99.46</u>	
14. Replication and Repair		
14.1 DNA polymerase PATH:hsa03030		
14.2 Replication Complex PATH:hsa03032		<u>5.99.1.3</u>
23626 SPO11	<u>5.99.1.3</u>	
7153 TOP2A, TOP2	<u>5.99.1.3</u>	
7155 TOP2B	<u>5.99.1.3</u>	
7156 TOP3A, TOP3	<u>5.99.1.2</u>	
8940 TOP3B	<u>5.99.1.2</u>	
22. Enzyme Complex		
22.1 Electron Transport System, Complex I PATH:hsa03100		
22.2 Electron Transport System, Complex II PATH:hsa03150		
22.3 Electron Transport System, Complex III PATH:hsa03140		
22.4 Electron Transport System, Complex IV PATH:hsa03130		
22.5 ATP Synthase PATH:hsa03110		
22.8 ATPases PATH:hsa03230		
23. Unassigned		
23.1 Enzymes		
5538 PPT1, CLN1, PPT, INCL	C160ACP + H2O → C160 + ACP	<u>3.1.2.22</u>
23.2 Non-enzymes		
22934 RPIA, RPI	RL5P <> R5P	<u>5.3.1.6</u>
5250 SLC25A3, PHC	PI + H <> Hm + Plm	
6576	CIT + MALm <> CITm + MAL	
51166 LOC51166	AADP + AKG → GLU + KADP	
5625 PRODH	PRO + FAD → P5C + FADH2	<u>2.6.1.39</u>
6517 SLC2A4, GLUT4	GLCxt → GLC	
6513 SLC2A1, GLUT1, GLUT	GLCxt → GLC	
26275 HIBCH, HIBYL-COA-H	HIBCOAm + H2O m → HIBm + COAm	
23305 KIAA0837, ACS2, LACS5, LACS2	C160 + COA + ATP → AMP + PPI + C160COA	
8611 PPAP2A, PAP-2A	PA + H2O → DAGLY + PI	
8612 PPAP2C, PAP-2C	PA + H2O → DAGLY + PI	
8613 PPAP2B, PAP-2B	PA + H2O → DAGLY + PI	
56994 LOC56994	CDPCHO + DAGLY → PC + CMP	
10400 PEMT, PEMT2	SAM + PE → SAH + PMME	
5833 PCYT2, ET	PETHM + CTP → CDPETN + PPI	
10390 CEPT1	CDPETN + DAGLY <> CMP + PE	
8394 PIP5K1A	PINS4P + ATP → D45PI + ADP	
8395 PIP5K1B, STM7, MSS4	PINS4P + ATP → D45PI + ADP	
8396 PIP5K2B	PINS4P + ATP → D45PI + ADP	
23396 PIP5K1C, KIAA0589, PIP5K-GAMMA	PINS4P + ATP → D45PI + ADP	
24. Our own reactions which need to be found in KEGG		

GL3P $\leftrightarrow$ GL3Pm	
T3P2 $\leftrightarrow$ T3P2m	
PYR $\leftrightarrow$ PYRm + Hm	
ADP + ATPm + PI + H $\rightarrow$ Hm + ADPm + ATP + Plm	
AKG + MALm $\leftrightarrow$ AKGm + MAL	
ASPm + GLU + H $\rightarrow$ Hm + GLUm + ASP	
GDP + GTPm + PI + H $\rightarrow$ Hm + GDPm + GTP + Plm	
C160Ax1 + FABP $\rightarrow$ C160FP + ALBxt	
C160FP $\rightarrow$ C160 + FABP	
C180Ax1 + FABP $\rightarrow$ C180FP + ALBxt	
C180FP $\rightarrow$ C180 + FABP	
C161Ax1 + FABP $\rightarrow$ C161FP + ALBxt	
C161FP $\rightarrow$ C161 + FABP	
C181Ax1 + FABP $\rightarrow$ C181FP + ALBxt	
C181FP $\rightarrow$ C181 + FABP	
C182Ax1 + FABP $\rightarrow$ C182FP + ALBxt	
C182FP $\rightarrow$ C182 + FABP	
C204Ax1 + FABP $\rightarrow$ C204FP + ALBxt	
C204FP $\rightarrow$ C204 + FABP	
O2xt $\rightarrow$ O2	
O2 $\leftrightarrow$ O2m	
ACTACm + SUCCOAm $\rightarrow$ SUCCm + AACCOAm	
3HB $\rightarrow$ 3HBm	
MGCOAm + H2Om $\rightarrow$ H3MCOAm	4.2.1.18
OMVAL $\rightarrow$ OMVALm	
OIVAL $\rightarrow$ OIVALm	
OICAP $\rightarrow$ OICAPm	
C160CAR $\leftrightarrow$ C160CARm	
CAR $\leftrightarrow$ CARm	
DMMCOAm $\rightarrow$ LMMCOAm	5.1.99.1
<b>amino acid metabolism</b>	
THR $\rightarrow$ NH3 + H2O + OBUT	4.2.1.16
THR + NAD $\rightarrow$ CO2 + NADH + AMA	1.1.1.103
THR + NAD + COA $\rightarrow$ NADH + ACCOA + GLY	
AASA + NAD $\rightarrow$ NADH + AADP	1.2.1.31
FKYN + H2O $\rightarrow$ FOR + KYN	3.5.1.9
CMUSA $\rightarrow$ CO2 + AM6SA	4.1.1.45
AM6SA + NAD $\rightarrow$ AMUCO + NADH	1.2.1.32
AMUCO + NADPH $\rightarrow$ KADP + NADP + NH4	1.5.1.-
CYSS + AKG $\leftrightarrow$ GLU + SPYR	
URO + H2O $\rightarrow$ 415P	4.2.1.49
415P + H2O $\rightarrow$ FIGLU	3.5.2.7
GLU $\leftrightarrow$ GLUm + Hm	
ORN + Hm $\rightarrow$ ORNm	
ORN + Hm + CITRm $\leftrightarrow$ CITR + ORNm	
GLU + ATP + NADPH $\rightarrow$ NADP + ADP + PI + GLUGSAL	
GLYAm + ATPm $\rightarrow$ ADPm + 2PGm	
AM6SA $\rightarrow$ PIC	
SPYR + H2O $\rightarrow$ H2SO3 + PYR	
P5C $\leftrightarrow$ GLUGSAL	
<b>fatty acid synthesis</b>	
MALCOA + ACP $\leftrightarrow$ MALACP + COA	2.3.1.39
ACCOA + ACP $\leftrightarrow$ ACACP + COA	
ACACP + 4 MALACP + 8 NADPH $\rightarrow$ 8 NADP + C100ACP + 4	
CO2 + 4 ACP	
ACACP + 5 MALACP + 10 NADPH $\rightarrow$ 10 NADP + C120ACP + 5	
CO2 + 5 ACP	
ACACP + 6 MALACP + 12 NADPH $\rightarrow$ 12 NADP + C140ACP + 6	
CO2 + 6 ACP	
ACACP + 6 MALACP + 11 NADPH $\rightarrow$ 11 NADP + C141ACP + 6	
CO2 + 6 ACP	
ACACP + 7 MALACP + 14 NADPH $\rightarrow$ 14 NADP + C160ACP + 7	
CO2 + 7 ACP	
ACACP + 7 MALACP + 13 NADPH $\rightarrow$ 13 NADP + C161ACP + 7	
CO2 + 7 ACP	

ACACP + 8 MALACP + 16 NADPH  $\rightarrow$  16 NADP + C180ACP + 8  
CO2 + 8 ACP  
ACACP + 8 MALACP + 15 NADPH  $\rightarrow$  15 NADP + C181ACP + 8  
CO2 + 8 ACP  
ACACP + 8 MALACP + 14 NADPH  $\rightarrow$  14 NADP + C182ACP + 8  
CO2 + 8 ACP  
C160COA + CAR  $\rightarrow$  C160CAR + COA  
C160CARm + COAm  $\rightarrow$  C160COAm + CARm

## fatty acid degradation

GL3P + 0.017 C100ACP + 0.062 C120ACP + 0.1 C140ACP +  
0.27 C160ACP + 0.169 C161ACP + 0.055 C180ACP + 0.235  
C181ACP + 0.093 C182ACP  $\rightarrow$  AGL3P + ACP  
TAGLYm + 3 H2Om  $\rightarrow$  GLm + 3 C160m

## Phospholipid metabolism

SAM + PMME  $\rightarrow$  SAH + PDME  
PDME + SAM  $\rightarrow$  PC + SAH  
PE + SER  $\leftrightarrow$  PS + ETHM

## Muscle contraction

MYOACT + ATP  $\rightarrow$  MYOATP + ACTIN  
MYOATP + ACTIN  $\rightarrow$  MYOADPAC  
MYOADPAC  $\rightarrow$  ADP + PI + MYOACT + CONTRACT

Table 2

```

// Homo Sapiens Core Metabolic Network //

// Glycolysis //
-1 GLC -1 ATP +1 G6P +1 ADP 0 HK1
-1 G6P -1 H2O +1 GLC +1 PI 0 G6PC
-1 G6P +1 F6P 0 GPIR
-1 F6P -1 ATP +1 FDP +1 ADP 0 PFKL
-1 FDP -1 H2O +1 F6P +1 PI 0 FBP1
-1 FDP +1 T3P2 +1 T3P1 0 ALDOAR
-1 T3P2 +1 T3P1 0 TPI1R
-1 T3P1 -1 PI -1 NAD +1 NADH +1 13PDG 0 GAPDR
-1 13PDG -1 ADP +1 3PG +1 ATP 0 PGK1R
-1 13PDG +1 23PDG 0 PGAM1
-1 23PDG -1 H2O +1 3PG +1 PI 0 PGAM2
-1 3PG +1 2PG 0 PGAM3R
-1 2PG +1 PEP +1 H2O 0 ENO1R
-1 PEP -1 ADP +1 PYR +1 ATP 0 PKLR
-1 PYRm -1 COAm -1 NADm +1 NADHm +1 CO2m +1 ACCOAm 0 PDHA1
-1 NAD -1 LAC +1 PYR +1 NADH 0 LDHAR
-1 G1P +1 G6P 0 PGM1R

// TCA //
-1 ACCOAm -1 OAm -1 H2Om +1 COAm +1 CITm 0 CS
-1 CIT +1 ICIT 0 ACO1R
-1 CITm +1 ICITm 0 ACO2R
-1 ICIT -1 NADP +1 NADPH +1 CO2 +1 AKG 0 IDH1
-1 ICITm -1 NADPm +1 NADPHm +1 CO2m +1 AKGm 0 IDH2
-1 ICITm -1 NADm +1 CO2m +1 NADHm +1 AKGm 0 IDH3A
-1 AKGm -1 NADm -1 COAm +1 CO2m +1 NADHm +1 SUCCOAm 0 OGDH
-1 GTPm -1 SUCCm -1 COAm +1 GDPm +1 PIm +1 SUCCOAm 0 SUCLG1R
-1 ATPm -1 SUCCm -1 COAm +1 ADPm +1 PIm +1 SUCCOAm 0 SUCLA2R
-1 FUMm -1 H2Om +1 MALm 0 FHR
-1 MAL -1 NAD +1 NADH +1 OA 0 MDH1R
-1 MALm -1 NADm +1 NADHm +1 OAm 0 MDH2R
-1 PYRm -1 ATPm -1 CO2m +1 ADPm +1 OAm +1 PIm 0 PC
-1 OA -1 GTP +1 PEP +1 GDP +1 CO2 0 PCK1
-1 OAm -1 GTPm +1 PEPm +1 GDPm +1 CO2m 0 PCK2
-1 ATP -1 CIT -1 COA -1 H2O +1 ADP +1 PI +1 ACCOA +1 OA 0
ACLY

```

```

// PPP //
-1 G6P -1 NADP +1 D6PGL +1 NADPH 0 G6PDR
-1 D6PGL -1 H2O +1 D6PGC 0 PGLS
-1 D6PGC -1 NADP +1 NADPH +1 CO2 +1 RL5P 0 PGD
-1 RL5P +1 X5P 0 RPER
-1 R5P -1 X5P +1 T3P1 +1 S7P 0 TKT1R
-1 X5P -1 E4P +1 F6P +1 T3P1 0 TKT2R
-1 T3P1 -1 S7P +1 E4P +1 F6P 0 TALDO1R
-1 RL5P +1 R5P 0 RPIAR

// Glycogen //
-1 G1P -1 UTP +1 UDPG +1 PPI 0 UGP1
-1 UDPG +1 UDP +1 GLYCOGEN 0 GYS1
-1 GLYCOGEN -1 PI +1 G1P 0 GBE1

// ETS //
-1 MALm -1 NADPm +1 CO2m +1 NADPHm +1 PYRm 0 ME3
-1 MALm -1 NADm +1 CO2m +1 NADHm +1 PYRm 0 ME2
-1 MAL -1 NADP +1 CO2 +1 NADPH +1 PYR 0 ME1
-1 NADHm -1 Qm -4 Hm +1 QH2m +1 NADm +4 H 0 MTND1
-1 SUCCm -1 FADm +1 FUMm +1 FADH2m 0 SDHC1R
-1 FADH2m -1 Qm +1 FADm +1 QH2m 0 SDHC2R
-1 O2m -4 FEROm -4 Hm +4 FERIm +2 H2Om +4 H 0 UQCREFS1
-1 QH2m -2 FERIm -4 Hm +1 Qm +2 FEROm +4 H 0 COX5BL4
-1 ADPm -1 PIm -3 H +1 ATPm +3 Hm +1 H2Om 0 MTAT
-1 ADP -1 ATPm -1 PI -1 H +1 Hm +1 ADPm +1 ATP +1 PIm 0 ATPMC
-1 GDP -1 GTPm -1 PI -1 H +1 Hm +1 GDPm +1 GTP +1 PIm 0 GTPMC
-1 PPI +2 PI 0 PP

-1 ACCOA -1 ATP -1 CO2 +1 MALCOA +1 ADP +1 PI 0 ACACAR
-1 GDP -1 ATP +1 GTP +1 ADP 0 GOT3R

// Transporters //
-1 CIT -1 MALm +1 CITm +1 MAL 0 CITMCR
-1 PYR -1 H +1 PYRm +1 Hm 0 PYRMCR

// Glycerol Phosphate Shuttle //
-1 GL3Pm -1 FADm +1 T3P2m +1 FADH2m 0 GPD2
-1 T3P2 -1 NADH +1 GL3P +1 NAD 0 GPD1
-1 GL3P +1 GL3Pm 0 GL3PMCR
-1 T3P2 +1 T3P2m 0 T3P2MCR

// Malate/Aspartate Shuttle //
-1 OAm -1 GLUm +1 ASPm +1 AKGm 0 GOT1R
-1 ASP -1 AKG +1 OA +1 GLU 0 GOT2R
-1 AKG -1 MALm +1 AKGm +1 MAL 0 MALMCR
-1 ASPm -1 GLU -1 H +1 Hm +1 GLUm +1 ASP 0 ASPMC

```

```
// Exchange Fluxes //
+1 GLC 0 GLCexR
+1 PYR 0 PYRexR
+1 CO2 0 CO2exR
+1 O2 0 O2exR
+1 PI 0 PIexR
+1 H2O 0 H2OexR
+1 LAC 0 LACexR

+1. CO2m 0 CO2min
-1 CO2m 0 CO2mout
+1 O2m 0 O2min
-1 O2m 0 O2mout
+1 H2Om 0 H2Omin
-1 H2Om 0 H2Omout
+1 PIIm 0 PImin
-1 PIIm 0 PIImout

// Output //
-1 ATP +1 ADP +1 PI 0 Output

0.0 end

end E 0

max
1 Output
0 end

0 GLCexR 1
-1000 PYRexR 0
-1000 LACexR 0

0 end 0
rev. rxn 33
nonrev. rxn 31
total rxn 64
matrix columns 97
unique enzymes 52
```

Table 3

Abbrev.	Reaction	Rxn Name
<i>Glycolysis</i>		
HK1	GLC + ATP $\rightarrow$ G6P + ADP	HK1
G6PC, G6PT	G6P + H2O $\rightarrow$ GLC + Pi	G6PC
GPI	G6P $\leftrightarrow$ F6P	GPI
PFKL	F6P + ATP $\rightarrow$ FDP + ADP	PFKL
FBP1, FBP	FDP + H2O $\rightarrow$ F6P + Pi	FBP1
ALDOA	FDP $\leftrightarrow$ T3P2 + T3P1	ALDOA
TPI1	T3P2 $\leftrightarrow$ T3P1	TPI1
GAPD, GAPDH	T3P1 + Pi + NAD $\leftrightarrow$ NADH + 13PDG	GAPD
PGK1, PGKA	13PDG + ADP $\leftrightarrow$ 3PG + ATP	PGK1
PGAM1, PGAMA	13PDG $\leftrightarrow$ 23PDG	PGAM1
	23PDG + H2O $\rightarrow$ 3PG + Pi	PGAM2
	3PG $\leftrightarrow$ 2PG	PGAM3
ENO1, PPH, ENO1L1	2PG $\leftrightarrow$ PEP + H2O	ENO1
PKLR, PK1	PEP + ADP $\rightarrow$ PYR + ATP	PKLR
PDHA1, PHE1A, PDHA	PYRm + COAm + NADm $\rightarrow$ NADHm + CO2m + ACCOAm	PDHA1
LDHA, LDH1	NAD + LAC $\leftrightarrow$ PYR + NADH	LDHA
PGM1	G1P $\leftrightarrow$ G6P	PGM1
TCA	ACCOAm + OA + H2Om $\rightarrow$ COAm + CITm	CS
CS	CIT $\leftrightarrow$ ICIT	ACO1
ACO1, IREB1, IRP1	CITm $\leftrightarrow$ ICITm	ACO2
ACO2	ICIT + NADP $\rightarrow$ NADPH + CO2 + AKG	IDH1
IDH1	ICITm + NADPm $\rightarrow$ NADPHm + CO2m + AKGm	IDH2
IDH2	ICITm + NADm $\rightarrow$ CO2m + NADHm + AKGm	IDH3A
IDH3A	AKGm + NADm + COAm $\rightarrow$ CO2m + NADHm + SUCCOAm	OGDH
OGDH	GTPm + SUCCm + COAm $\leftrightarrow$ GDPm + PIm + SUCCOAm	SUCLG1
SUCLG1, SUCLA1	ATPm + SUCCm + COAm $\leftrightarrow$ ADPm + PIm + SUCCOAm	SUCLA2
SUCLA2	FUMm + H2Om $\leftrightarrow$ MALm	FH
FH	MAL + NAD $\leftrightarrow$ NADH + OA	MDH1
MDH1	MALm + NADm $\leftrightarrow$ NADHm + OA	MDH2
MDH2	PYRm + ATPm + CO2m $\rightarrow$ ADPm + OA + PIm	PC
PC, PCB	ATP + CIT + COA + H2O $\rightarrow$ ADP + Pi + ACCOA + OA	ACLY
ACLY, ATPCL, CLATP	OA + GTP $\rightarrow$ PEP + GDP + CO2	PCK1
PCK1		
<i>PPP</i>		
G6PD, G6PD1	G6P + NADP $\leftrightarrow$ D6PGL + NADPH	G6PD
PGLS, 6PGL	D6PGL + H2O $\rightarrow$ D6PGC	PGLS
PGD	D6PGC + NADP $\rightarrow$ NADPH + CO2 + RL5P	PGD
RPE	RL5P $\leftrightarrow$ X5P	RPE
TKT	R5P + X5P $\leftrightarrow$ T3P1 + S7P	TKT1
	X5P + E4P $\leftrightarrow$ F6P + T3P1	TKT2
TALDO1	T3P1 + S7P $\leftrightarrow$ E4P + F6P	TALDO1
UGP1	G1P + UTP $\rightarrow$ UDPG + PPI	UGP1
ACACA, ACAC, ACC	ACCOA + ATP + CO2 $\leftrightarrow$ MALCOA + ADP + Pi + H	ACACA
ETS		
ME3	MALm + NADPm $\rightarrow$ CO2m + NADPHm + PYRm	ME3
MTND1	NADHm + Qm + 4 Hm $\rightarrow$ QH2m + NADm + 4 H	MTND1
SDHC	SUCCm + FADm $\leftrightarrow$ FUMm + FADH2m	SDHC1
	FADH2m + Qm $\leftrightarrow$ FADm + QH2m	SDHC2
UQCRRFS1, RJS1	FADH2m + 4 Hm $\rightarrow$ 4 FERIm + 2 H2Om + 4 H	UQCRRFS1
COX5BL4	O2m + 4 FEROm + 4 Hm $\rightarrow$ 4 FERIm + 2 H2Om + 4 H	COX5BL4
MTATP6	QH2m + 2 FERIm + 4 Hm $\rightarrow$ Qm + 2 FEROm + 4 H	MTAT
PP, SID6-8061	ADPm + PIm + 3 H $\rightarrow$ ATPm + 3 Hm + H2Om	PP
	PPI $\rightarrow$ 2 Pi	
<i>Malate Aspartate shuttle</i>		
GOT1	OA + GLUm $\leftrightarrow$ ASPm + AKGm	GOT1
GOT2	OA + GLU $\leftrightarrow$ ASP + AKG	GOT2
	GDP + ATP $\leftrightarrow$ GTP + ADP	GOT3

**Glycogen**

GBE1 GLYCOGEN + PI  $\rightarrow$  G1P  
 GYS1, GYS UDPG  $\rightarrow$  UDP + GLYCOGEN

GBE1  
 GYS1

**Glycerol Phosphate Shuttle**

GPD2 GL3Pm + FADm  $\rightarrow$  T3P2m + FADH2m  
 GPD1 T3P2 + NADH  $\rightarrow$  GL3P + NAD  
 RPIA, RPI RLSP  $\leftrightarrow$  R5P

GPD2  
 GPD1  
 RPIA

**Mitochondria Transport**

CIT + MALm  $\leftrightarrow$  CITm + MAL  
 GL3P  $\leftrightarrow$  GL3Pm  
 T3P2  $\leftrightarrow$  T3P2m  
 PYR  $\leftrightarrow$  PYRm + Hm  
 ADP + ATPm + PI + H  $\rightarrow$  Hm + ADPm + ATP + Pi<sub>m</sub>  
 AKG + MALm  $\leftrightarrow$  AKGm + MAL  
 ASPm + GLU + H  $\rightarrow$  Hm + GLUm + ASP  
 GDP + GTPm + PI + H  $\rightarrow$  Hm + GDPm + GTP + Pi<sub>m</sub>

CITMC  
 GL3PMC  
 T3P2MC  
 PYRMC  
 ATPMC  
 MALMC  
 ASPMC  
 GTPMC

**TABLE 4**  
Metabolic Reaction for Muscle Cells

Reaction	Rxd Name
GLC + ATP $\rightarrow$ G6P + ADP	0 HK1
G6P $\leftrightarrow$ F6P	0 GPI
F6P + ATP $\rightarrow$ FDP + ADP	0 PFKL1
FDP + H2O $\rightarrow$ F6P + Pi	0 FBP1
FDP $\leftrightarrow$ T3P2 + T3P1	0 ALDOA
T3P2 $\leftrightarrow$ T3P1	0 TP1
T3P1 + Pi + NAD $\leftrightarrow$ NADH + 13PDG	0 GAPD
13PDG + ADP $\leftrightarrow$ 3PG + ATP	0 PGK1
3PG $\leftrightarrow$ 2PG	0 PGAM3
2PG $\leftrightarrow$ PEP + H2O	0 ENO1
PEP + ADP $\rightarrow$ PYR + ATP	0 PK1
PYRm + COAm + NADm $\rightarrow$ + NADHm + CO2m + ACCOAm	0 PDHA1
NAD + LAC $\leftrightarrow$ PYR + NADH	0 LDHA
G1P $\leftrightarrow$ G6P	0 PGM1
ACCOAm + OAm + H2Om $\rightarrow$ COAm + CITm	0 CS
CIT $\leftrightarrow$ ICIT	0 ACO1
CITm $\leftrightarrow$ ICITm	0 ACO2
ICITm + NADP $\rightarrow$ NADPH + CO2 + AKG	0 IDH1
ICITm + NADPm $\rightarrow$ NADPHm + CO2m + AKGm	0 IDH2
ICITm + NADm $\rightarrow$ CO2m + NADHm + AKGm	0 IDH3A
AKGm + NADm + COAm $\rightarrow$ CO2m + NADHm + SUCCOAm	0 CGDH
GTPm + SUCCm + COAm $\leftrightarrow$ GDPm + PIm + SUCCOAm	0 SUCLG1
GTPm + SUCCm + COAm $\leftrightarrow$ ADPm + PIm + SUCCOAm	0 SUCLG2
ATPm + SUCCm + COAm $\leftrightarrow$ ADPm + PIm + SUCCOAm	0 FH
FUMm + H2Om $\leftrightarrow$ MALm	0 MDH1
MAL + NAD $\leftrightarrow$ NADH + OA	0 MDH2
MALm + NADm $\leftrightarrow$ NADHm + OAm	0 PC
PYRm + ATPm + CO2m $\rightarrow$ ADPm + OAm + PIm	0 ACLY
ATP + CIT + COA + H2O $\rightarrow$ ADP + Pi + ACCOA + OA	0 PCK1
OA + GTP $\rightarrow$ PEP + GDP + CO2	0 PCK2
OAm + GTPm $\rightarrow$ PEPm + GDPm + CO2m	0 G6PD
G6P + NADP $\leftrightarrow$ D6PGL + NADPH	0 H6PD
D6PGL + H2O $\rightarrow$ D6PGC	0 PGD
D6PGC + NADP $\rightarrow$ NADPH + CO2 + RL5P	0 RPE
RL5P $\leftrightarrow$ X5P	0 TKT1
R5P + X5P $\leftrightarrow$ T3P1 + S7P	0 TKT2
X5P + E4P $\leftrightarrow$ F6P + T3P1	0 TALDO1
T3P1 + S7P $\leftrightarrow$ E4P + F6P	0 RPIA
RL5P $\leftrightarrow$ R5P	0 UGP1
G1P + UTP $\rightarrow$ UDPG + PPI	0 GBE1
GLYCOGEN + Pi $\rightarrow$ G1P	0 GYS1
UDPG $\rightarrow$ UDP + GLYCOGEN	0 ME2
MALm + NADm $\rightarrow$ CO2m + NADHm + PYRm	0 ME3
MALm + NADPm $\rightarrow$ CO2m + NADPHm + PYRm	0 HUMNDME
MAL + NADP $\rightarrow$ CO2 + NADPH + PYR	0 MTND1
NADHm + Qm + 4 Hm $\rightarrow$ QH2m + NADm + 4 H	0 SDHC1
SUCCm + FADm $\leftrightarrow$ FUMm + FADH2m	0 SDHC2
FADH2m + Qm $\leftrightarrow$ FADm + QH2m	0 UQCRCFS1
Q2m + 4 FEROm + 4 Hm $\rightarrow$ 4 FERIm + 2 H2Om + 4 H	0 COX5BL4
QH2m + 2 FERIm + 4 Hm $\rightarrow$ Qm + 2 FEROm + 4 H	0 MTAT1
ADPm + PIm + 3 H $\rightarrow$ ATPm + 3 Hm + H2Om	0 ATPMC
ADP + ATPm + Pi + H $\rightarrow$ Hm + ADPm + ATP + PIm	0 GTPMC
GDP + GTPm + Pi + H $\rightarrow$ Hm + GDPm + GTP + PIm	0 PP
PPI $\rightarrow$ 2 Pi	0 NME1
GDP + ATP $\leftrightarrow$ GTP + ADP	0 ACACA
ACCOA + ATP + CO2 $\leftrightarrow$ MALCOA + ADP + Pi + H	0 FAS1_1
MALCOA + ACP $\leftrightarrow$ MALACP + COA	0 FAS1_2
ACCOA + ACP $\leftrightarrow$ ACACP + COA	
ACACP + 4 MALACP + 8 NADPH $\rightarrow$ 8 NADP + C100ACP + 4 CO2 + 4 ACP	0 C100SY
ACACP + 5 MALACP + 10 NADPH $\rightarrow$ 10 NADP + C120ACP + 5 CO2 + 5	0 C120SY
ACP	
ACACP + 6 MALACP + 12 NADPH $\rightarrow$ 12 NADP + C140ACP + 6 CO2 + 6	0 C140SY
ACP	
ACACP + 6 MALACP + 11 NADPH $\rightarrow$ 11 NADP + C141ACP + 6 CO2 + 6	0 C141SY
ACP	
ACACP + 7 MALACP + 14 NADPH $\rightarrow$ 14 NADP + C160ACP + 7 CO2 + 7	0 C160SY
ACP	
ACACP + 7 MALACP + 13 NADPH $\rightarrow$ 13 NADP + C161ACP + 7 CO2 + 7	0 C161SY
ACP	
ACACP + 8 MALACP + 16 NADPH $\rightarrow$ 16 NADP + C180ACP + 8 CO2 + 8	0 C180SY
ACP	
ACACP + 8 MALACP + 15 NADPH $\rightarrow$ 15 NADP + C181ACP + 8 CO2 + 8	0 C181SY
ACP	
ACACP + 8 MALACP + 14 NADPH $\rightarrow$ 14 NADP + C182ACP + 8 CO2 + 8	0 C182SY
ACP	
C160ACP + H2O $\rightarrow$ C160 + ACP	0 PPT1
C160 + COA + ATP $\rightarrow$ AMP + PPI + C160COA	0 KIAA

C160COA + CAR $\rightarrow$ C160CAR + COA	0 C160CA
C160CARm + COAm $\rightarrow$ C160COAm + CARm	0 C160CB
C160CARm + COAm + FADm + NADm $\rightarrow$ FADH2m + NADHm +	0 HADHA
C140COAm + ACCOAm	0 HADH2
C140COAm + 7 COAm + 7 FADm + 7 NADm $\rightarrow$ 7 FADH2m + 7 NADHm + 7	0 TAGRXN
ACCOAm	0 GAT1
TAGLYm + 3 H20m $\rightarrow$ GLm + 3 C160m	0 AGPAT1
GL3P + 0.017 C100ACP + 0.062 C120ACP + 0.1 C140ACP + 0.27	0 CHKL1
C160ACP + 0.169 C161ACP + 0.055 C180ACP + 0.235 C181ACP + 0.093	0 PCYT1A
C182ACP $\rightarrow$ AGL3P + ACP	0 LDC
AGL3P + 0.017 C100ACP + 0.062 C120ACP + 0.100 C140ACP + 0.270	0 PEMT
C160ACP + 0.169 C161ACP + 0.055 C180ACP + 0.235 C181ACP + 0.093	0 MFPS
C182ACP $\rightarrow$ PA + ACP	0 PNMNM
ATP + CHO $\rightarrow$ ADP + PCHO	0 ISYNA1
PCHO + CTP $\rightarrow$ CDPCHO + PPI	0 IMPA1
CDPCHO + DAGLY $\rightarrow$ PC + CMP	0 CDS1
SAM + PE $\rightarrow$ SAH + PMME	0 PIS
SAM + PMME $\rightarrow$ SAH + PDME	0 PIK3CA
PDME + SAM $\rightarrow$ PC + SAH	0 PIK4CA
GSP $\rightarrow$ M1P	0 PIP5K1
M1P $\rightarrow$ MYO1 + PI	0 PLCB2
PA + CTP $\leftrightarrow$ CDPDG + PPI	0 PPAP2A
CDPDG + MYO1 $\rightarrow$ CMP + PINS	0 DGAT
ATP + PINS $\rightarrow$ ADP + PINSP	0 PTDS
ATP + PINS $\rightarrow$ ADP + PINS4P	0 CEPT1
PINS4P + ATP $\rightarrow$ D45P1 + ADP	0 PESER
D45P1 $\rightarrow$ TPI + DAGLY	0 EK1
PA + H2O $\rightarrow$ DAGLY + PI	0 PCYT2
DAGLY + 0.017 C100ACP + 0.062 C120ACP + 0.100 C140ACP + 0.270	0 PISD
C160ACP + 0.169 C161ACP + 0.055 C180ACP + 0.235 C181ACP + 0.093	0 BDH
C182ACP $\rightarrow$ TAGLY + ACP	0 3OCT
CDPDG + SER $\leftrightarrow$ CMP + PS	0 SHMT1
CDPETN + DAGLY $\leftrightarrow$ CMP + PE	0 SHMT2
PE + SER $\leftrightarrow$ PS + ETHM	0 AGXT
ATP + ETHM $\rightarrow$ ADP + PETHM	0 PHGDH
PETHM + CTP $\rightarrow$ CDPETN + PPI	0 PSA
PS $\rightarrow$ PE + CO2	0 PSPH
3HBm + NADm $\rightarrow$ NADHm + Hm + ACTACm	0 GLYD
ACTACm + SUCCOAm $\rightarrow$ SUCCm + AACOAm	0 SDS
THF + SER $\leftrightarrow$ GLY + METTHF	0 GLTK
THFm + SERm $\leftrightarrow$ GLYm + METTHFm	0 GPT
SERm + PYRm $\leftrightarrow$ ALAm + 3HPm	0 CPS1
3PG + NAD $\leftrightarrow$ NADH + PHP	0 GLUD1
PHP + GLU $\leftrightarrow$ AKG + 3PSER	0 GLUD2
3PSER + H2O $\rightarrow$ PI + SER	0 GLUJ
3HPm + NADHm $\rightarrow$ NADm + GLYAm	0 ASNS
SER $\rightarrow$ PYR + NH3 + H2O	0 OAT
GLYAm + ATPm $\rightarrow$ ADPm + 2PGm	0 GLUMT
PYR + GLU $\leftrightarrow$ AKG + ALA	0 PSCS
GLUm + CO2m + 2 ATPm $\rightarrow$ 2 ADPm + 2 Pi + CAPm	0 PYCS
AKGm + NADHm + NH3m $\leftrightarrow$ NADm + H20m + GLUm	0 SPTC
AKGm + NADPHm + NH3m $\leftrightarrow$ NADPm + H20m + GLUm	0 HAL
GLUm + NH3m + ATPm $\rightarrow$ GLNm + ADPm + Pi	0 UROH
ASPM + ATPm + GLNm $\rightarrow$ GLUm + ASNm + AMPm + PPIm	0 IMPR
ORN + AKG $\leftrightarrow$ GLUGSAL + GLU	0 FTCD
GLU $\leftrightarrow$ GLUm + Hm	0 MAT1A
GLU + ATP + NADPH $\rightarrow$ NADP + ADP + Pi + GLUGSAL	0 DNMT1
GLUP + NADH $\rightarrow$ NAD + Pi + GLUGSAL	0 AHCYL1
PSC $\leftrightarrow$ GLUGSAL	0 MTR
HIS $\rightarrow$ NH3 + URO	0 CBS
URO + H2O $\rightarrow$ 415P	0 CTH1
415P + H2O $\rightarrow$ FIGLU	0 CTH2
FIGLU + THF $\rightarrow$ NFTHF + GLU	0 CDO1
MET + ATP + H2O $\rightarrow$ PPi + Pi + SAM	0 CYSAT
SAM + DNA $\rightarrow$ SAH + DNASMC	0 SPTB
SAH + H2O $\rightarrow$ HCYS + ADN	0 LKRI
HCYS + MTHF $\rightarrow$ THF + MET	0 LKR2
SER + HCYS $\rightarrow$ LLCT + H2O	0 2ASD
LLCT + H2O $\rightarrow$ CYS + HSER	0 LOC5
OBUT + NH3 $\leftrightarrow$ HSER	0 TDO2
CYS + O2 $\leftrightarrow$ CYSS	0 KYNF
CYSS + AKG $\leftrightarrow$ GLU + SPYR	0 KMO
SPYR + H2O $\rightarrow$ H2SO3 + PYR	0 KYNU2
LYS + NADPH + AKG $\rightarrow$ NADP + H2O + SAC	
SAC + H2O + NAD $\rightarrow$ GLU + NADH + AASA	
AASA + NAD $\rightarrow$ NADH + AADP	
AADP + AKG $\rightarrow$ GLU + KADP	
TRP + O2 $\rightarrow$ RYK	
RYK + H2O $\rightarrow$ FOR + KYN	
KYN + NADPH + O2 $\rightarrow$ RYK + NADP + H2O	
RYK + H2O $\rightarrow$ HAN + ALA	

HAN + O2 -> CMUSA	0 HAAO
CMUSA -> CO2 + AM6SA	0 ACSD
AM6SA -> PIC	0 SPTA
AM6SA + NAD -> AMUCO + NADH	0 AMSD
AMUCO + NADPH -> KADP + NADP + NH4	0 2AMR
ARG -> ORN + UREA	0 ARG2
ORN + Hm -> ORNm	0 ORNIMT
ORN + Hm + CITRm <-> CITR + ORNm	0 ORNCITT
ORNm + CAPm -> CITRm + Pim + Hm	0 OTC
CITR + ASP + ATP <-> AMP + PPI + ARGSSUCC	0 ASS
ARGSSUCC -> FUM + ARG	0 ASL
PRO + FAD -> P5C + FADH2	0 PRODH
P5C + NADPH -> PRO + NADP	0 PYCR1
THR -> NH3 + H2O + OBUT	0 WTDH
THR + NAD -> CO2 + NADH + AMA	0 TDH
AMA + H2O + FAD -> NH3 + FADH2 + MTHGXL	0 MAOA
GLYm + THFm + NADm <-> METTHFm + NADHm + CO2m + NH3m	0 AMT
PHE + THBP + O2 -> TYR + DHBP + H2O	0 PAH
NADPH + DHBP -> NADP + THBP	0 QDPR
AKG + TYR -> HPHPYR + GLU	0 TAT
HPHPYR + O2 -> HGTs + CO2	0 HPD
HGTs + O2 -> MACA	0 HGD
MACA -> FACA	0 GSTZ1
FACA + H2O -> FUM + ACA	0 FAH
AKG + ILE -> OMVAL + GLU	0 BCAT1A
OMVALm + COAm + NADm -> MBCOAm + NADHm + CO2m	0 BCKDHA
MBCOAm + FADm -> MCCOAm + FADH2m	0 ACADMA
MCCOAm + H2Om -> MHVCOAm	0 ECHS1B
MHVCOAm + NADm -> MAACOAm + NADHm	0 EHHADHA
MAACOAm -> ACCOAm + PROPCOAm	0 ACAA2
2 ACCOAm <-> COAm + AACCOAm	0 ACATm1
AKG + VAL -> OVAL + GLU	0 BCAT1B
OVALm + COAm + NADm -> IBCOAm + NADHm + CO2m	0 BCKDHB
IBCOAm + FADm -> MACOAm + FADH2m	0 ACADSB
MACOAm + H2Om -> HIBCOAm	0 EHHADHC
HIBCOAm + H2Om -> HIBm + COAm	0 HIBCHA
HIBm + NADm -> MMAm + NADHm	0 EHHADHB
MMAm + COAm + NADm -> NADHm + CO2m + PROPCOAm	0 MMSDH
PROPCOAm + CO2m + ATPm -> ADPm + Pim + DMMCOAm	0 PCCA
DMMCOAm -> LMMCOAm	0 HIBCHF
LMMCOAm -> SUCCOAm	0 MUT
AKG + LEU -> OICAP + GLU	0 BCKDHA
OICAPm + COAm + NADm -> IVCOAm + NADHm + CO2m	0 BCKDHB
OICAPm + COAm + NADH -> IVCOAm + NADHm + CO2m	0 DBTC
OICAPm + COAm + NADHm -> IVCOAm + NADHm + CO2m	0 IVD
IVCOAm + FADm -> MCRCOAm + FADH2m	0 MCCC1
MCRCOAm + ATPm + CO2m + H2Om -> MGCOAm + ADPm + Pim	0 HIBCHB
MGCOAm + H2Om -> H3MCOAm	0 HMGCL
H3MCOAm -> ACCOAm + ACTACm	0 MYOSA
MYOACT + ATP -> MYOATP + ACTIN	0 MYOSB
MYOATP + ACTIN -> MYOADPAC	0 MYOSC
MYOADPAC -> ADP + Pi + MYOACT + CONTRACT	0 CREATA
PCRE + ADP -> CRE + ATP	0 CREATB
AMP + H2O -> Pi + ADN	0 CREATC
ATP + AMP <-> 2 ADP	0 C2MT
O2 <-> O2m	0 HBMT
3HB -> 3Hbm	0 CITMC
CIT + MALm <-> CITm + MAL	0 PYRMC
PYR <-> PYRm + Hm	0 C160CM
C160CAR + COAm -> C160COAm + CAR	0 HIBCHC
OMVAL -> OMVALm	0 HIBCHD
OIVAL -> OIVALm	0 HIBCHE
OICAP -> OICAPm	0 GLMT
GL <-> GLm	0 GPD2
GL3Pm + FADm -> T3P2m + FADH2m	0 GPD1
T3P2 + NADH <-> GL3P + NAD	0 GL3PMC
GL3P <-> GL3Pm	0 T3P2MC
T3P2 <-> T3P2m	0 GOT1
OA + GLUm <-> ASPm + AKGm	0 GOT2
OA + GLU <-> ASP + AKG	0 MALMC
AKG + MALm <-> AKGm + MAL	0 ASPMC
ASPM + GLU + H -> Hm + GLUm + ASP	0 GLUT4
GLCxt -> GLC	0 C2UP
O2x1 -> O2	0 FAT1
C160Axt + FABP -> C160FP + ALBxt	0 FAT2
C160FP -> C160 + FABP	0 FAT3
C180Axt + FABP -> C180FP + ALBxt	0 FAT4
C180FP -> C180 + FABP	0 FAT5
C161Axt + FABP -> C161FP + ALBxt	0 FAT6
C161FP -> C161 + FABP	0 FAT7
C181Axt + FABP -> C181FP + ALBxt	

C181FP $\rightarrow$ C181 + FABP	0 FAT8
C182Axd + FABP $\rightarrow$ C182FP + ALBxt	0 FAT9
C182FP $\rightarrow$ C182 + FABP	0 FAT10
C204Axd + FABP $\rightarrow$ C204FP + ALBxt	0 FAT11
C204FP $\rightarrow$ C204 + FABP	0 FAT12
PYRd + HEXT $\leftrightarrow$ PYR + H	0 PYRUP
LACxd + HEXT $\leftrightarrow$ LAC + HEXT	0 LACUP
H $\leftrightarrow$ HEXT	0 HexUP
CO2 $\leftrightarrow$ CO2m	0 CO2MT
H2O $\leftrightarrow$ H2O <sub>m</sub>	0 H2O <sub>MT</sub>
ATP + AC + COA $\rightarrow$ AMP + PPI + ACCOA	0 FL <sub>J2</sub>
C160CAR $\leftrightarrow$ C160CARm	0 C160MT
CARm $\leftrightarrow$ CAR	0 CARMT
CO2d $\leftrightarrow$ CO2	0 CO2UP
H2Oxt $\leftrightarrow$ H2O	0 H2OUP
PIxt + HEXT $\leftrightarrow$ HEXT + PI	0 PIUP
$\leftrightarrow$ GLCxt	0 GLCexR
$\leftrightarrow$ PYRxt	0 PYRexR
$\leftrightarrow$ CO2xt	0 CO2exR
$\leftrightarrow$ O2xt	0 O2exR
$\leftrightarrow$ PIxt	0 PlexR
$\leftrightarrow$ H2Oxt	0 H2OexR
$\leftrightarrow$ LACxt	0 LACexR
$\leftrightarrow$ C160Axt	0 C160AexR
$\leftrightarrow$ C161Axt	0 C161AexR
$\leftrightarrow$ C180Axt	0 C180AexR
$\leftrightarrow$ C181Axt	0 C181AexR
$\leftrightarrow$ C182Axt	0 C182AexR
$\leftrightarrow$ C204Axt	0 C204AexR
$\leftrightarrow$ ALBxt	0 ALBexR
$\leftrightarrow$ 3HB	0 HBexR
$\leftrightarrow$ GLYCOGEN	0 GLYex
$\leftrightarrow$ PCRE	0 PCREex
$\leftrightarrow$ TAGLYm	0 TAGmex
$\leftrightarrow$ ILE	0 ILEex
$\leftrightarrow$ VAL	0 VAlex
$\leftrightarrow$ CRE	0 CREex
$\leftrightarrow$ ADN	0 ADNex
$\leftrightarrow$ PI	0 Plex

What is claimed is:

1. A computer readable medium or media, comprising:
  - (a) a data structure relating a plurality of *Homo sapiens* reactants to a plurality of *Homo sapiens* reactions,  
5 wherein each of said *Homo sapiens* reactions comprises a reactant identified as a substrate of the reaction, a reactant identified as a product of the reaction and a stoichiometric coefficient relating said substrate and said product,  
10 wherein at least one of said *Homo sapiens* reactions is annotated to indicate an associated gene;
    - (b) a gene database comprising information characterizing said associated gene;  
15 (c) a constraint set for said plurality of *Homo sapiens* reactions, and  
20 (d) commands for determining at least one flux distribution that minimizes or maximizes an objective function when said constraint set is applied to said data representation, wherein said at least one flux distribution is predictive of a *Homo sapiens* physiological function.
2. The computer readable medium or media of claim 1, wherein said plurality of *Homo sapiens* reactions comprises at least one reaction from a peripheral metabolic pathway.  
25
3. The computer readable medium or media of

claim 2, wherein said peripheral metabolic pathway is selected from the group consisting of amino acid biosynthesis, amino acid degradation, purine biosynthesis, pyrimidine biosynthesis, lipid biosynthesis, fatty acid metabolism, cofactor biosynthesis and transport processes.

4. The computer readable medium or media of claim 1, wherein said *Homo sapiens* physiological function is selected from the group consisting of 10 growth, energy production, redox equivalent production, biomass production, production of biomass precursors, production of a protein, production of an amino acid, production of a purine, production of a pyrimidine, production of a lipid, production of a fatty acid, 15 production of a cofactor, transport of a metabolite, and consumption of carbon, nitrogen, sulfur, phosphate, hydrogen or oxygen.

5. The computer readable medium or media of claim 1, wherein said *Homo sapiens* physiological function is selected from the group consisting of 20 degradation of a protein, degradation of an amino acid, degradation of a purine, degradation of a pyrimidine, degradation of a lipid, degradation of a fatty acid and degradation of a cofactor.

25 6. The computer readable medium or media of claim 1, wherein said data structure comprises a set of linear algebraic equations.

7. The computer readable medium or media of claim 1, wherein said data structure comprises a 30 matrix.

8. The computer readable medium or media of  
claim 1, wherein said commands comprise an optimization  
problem.

9. The computer readable medium or media of  
5 claim 1, wherein said commands comprise a linear  
program.

10. The computer readable medium or media of  
claim 1, wherein at least one reactant in said  
plurality of *Homo sapiens* reactants or at least one  
10 reaction in said plurality of *Homo sapiens* reactions is  
annotated with an assignment to 'a subsystem or  
compartment.

11. The computer readable medium or media of  
claim 10, wherein a first substrate or product in said  
15 plurality of *Homo sapiens* reactions is assigned to a  
first compartment and a second substrate or product in  
said plurality of *Homo sapiens* reactions is assigned to  
a second compartment.

20 12. The computer readable medium or media of  
claim 1, wherein a plurality of said *Homo sapiens*  
reactions is annotated to indicate a plurality of  
associated genes and wherein said gene database  
comprises information characterizing said plurality of  
25 associated genes.

13. A computer readable medium or media,  
comprising:  
30 (a) a data structure relating a plurality of  
*Homo sapiens* reactants to a plurality of *Homo sapiens*  
reactions,

wherein each of said *Homo sapiens* reactions comprises a reactant identified as a substrate of the reaction, a reactant identified as a product of the reaction and a stoichiometric coefficient relating said 5 substrate and said product,

wherein at least one of said *Homo sapiens* reactions is a regulated reaction;

(b) a constraint set for said plurality of *Homo sapiens* reactions, wherein said constraint set 10 includes a variable constraint for said regulated reaction, and

(c) commands for determining at least one flux distribution that minimizes or maximizes an objective function when said constraint set is applied 15 to said data representation, wherein said at least one flux distribution is predictive of a *Homo sapiens* physiological function.

14. The computer readable medium or media of claim 13, wherein said variable constraint is dependent 20 upon the outcome of at least one reaction in said data structure.

15. The computer readable medium or media of claim 13, wherein said variable constraint is dependent upon the outcome of a regulatory event.

25 16. The computer readable medium or media of claim 13, wherein said variable constraint is dependent upon time.

17. The computer readable medium or media of

claim 13, wherein said variable constraint is dependent upon the presence of a biochemical reaction network participant.

5 18. The computer readable medium or media of claim 17, wherein said participant is selected from the group consisting of a substrate, product, reaction, protein, macromolecule, enzyme and gene.

10 19. The computer readable medium or media of claim 13, wherein a plurality of said reactions are regulated reactions and said constraints for said regulated reactions comprise variable constraints.

20. A computer readable medium or media, 15 comprising:

(a) a data structure relating a plurality of *Homo sapiens* skeletal muscle cell reactants to a plurality of *Homo sapiens* skeletal muscle cell reactions, wherein each of said *Homo sapiens* reactions comprises a reactant identified as a substrate of the reaction, a reactant identified as a product of the reaction and a stoichiometric coefficient relating said substrate and said product;

20 (b) a constraint set for said plurality of *Homo sapiens* reactions, and

25 (c) commands for determining at least one flux distribution that minimizes or maximizes an objective function when said constraint set is applied to said data representation, wherein said at least one flux distribution is predictive of *Homo sapiens* skeletal muscle cell energy production.

30 21. A method for predicting a *Homo sapiens* physiological function, comprising:

(a) providing a data structure relating a plurality of *Homo sapiens* reactants to a plurality of *Homo sapiens* reactions,

5 wherein each of said *Homo sapiens* reactions comprises a reactant identified as a substrate of the reaction, a reactant identified as a product of the reaction and a stoichiometric coefficient relating said substrate and said product,

10 wherein at least one of said *Homo sapiens* reactions is annotated to indicate an associated gene;

(b) providing a constraint set for said plurality of *Homo sapiens* reactions;

(c) providing an objective function, and

(d) determining at least one flux

15 distribution that minimizes or maximizes said objective function when said constraint set is applied to said data structure, thereby predicting a *Homo sapiens* physiological function related to said gene.

22. The method of claim 21, wherein said 20 plurality of *Homo sapiens* reactions comprises at least one reaction from a peripheral metabolic pathway.

23. The method of claim 22, wherein said peripheral metabolic pathway is selected from the group consisting of amino acid biosynthesis, amino acid 25 degradation, purine biosynthesis, pyrimidine biosynthesis, lipid biosynthesis, fatty acid metabolism, cofactor biosynthesis and transport processes.

24. The method of claim 21, wherein said 30 *Homo sapiens* physiological function is selected from the group consisting of growth, energy production,

redox equivalent production, biomass production, production of biomass precursors, production of a protein, production of an amino acid, production of a purine, production of a pyrimidine, production of a 5 lipid, production of a fatty acid, production of a cofactor, transport of a metabolite, and consumption of carbon, nitrogen, sulfur, phosphate, hydrogen or oxygen.

25. The method of claim 21, wherein said 10 *Homo sapiens* physiological function is selected from the group consisting of glycolysis, the TCA cycle, pentose phosphate pathway, respiration, biosynthesis of an amino acid, degradation of an amino acid, biosynthesis of a purine, biosynthesis of a pyrimidine, 15 biosynthesis of a lipid, metabolism of a fatty acid, biosynthesis of a cofactor, transport of a metabolite and metabolism of a carbon source, nitrogen source, oxygen source, phosphate source, hydrogen source or sulfur source.

20 26. The method of claim 21, wherein said data structure comprises a set of linear algebraic equations.

25 27. The method of claim 21, wherein said data structure comprises a matrix.

28. The method of claim 21, wherein said flux distribution is determined by linear programming.

29. The method of claim 21, further comprising:

(e) providing a modified data structure, wherein said modified data structure comprises at least 5 one added reaction, compared to the data structure of part (a), and

(f) determining at least one flux distribution that minimizes or maximizes said objective function 10 when said constraint set is applied to said modified data structure, thereby predicting a *Homo sapiens* physiological function.

30. The method of claim 29, further comprising

15 identifying at least one participant in said at least one added reaction.

31. The method of claim 30, wherein said identifying at least one participant comprises 20 associating a *Homo sapiens* protein with said at least one reaction.

32. The method of claim 31, further comprising

identifying at least one gene that encodes said protein.

25 33. The method of claim 30, further comprising

identifying at least one compound that alters the activity or amount of said at least one participant, thereby identifying a candidate drug or agent that 30 alters a *Homo sapiens* physiological function.

34. The method of claim 21, further comprising:

(e) providing a modified data structure, wherein said modified data structure lacks at least one reaction compared to the data structure of part (a),  
5 and

(f) determining at least one flux distribution

that minimizes or maximizes said objective function  
10 when said constraint set is applied to said modified data structure, thereby predicting a *Homo sapiens* physiological function.

35. The method of claim 34, further comprising  
15 identifying at least one participant in said at least one reaction.

36. The method of claim 35, wherein said identifying at least one participant comprises  
associating a *Homo sapiens* protein with said at least  
20 one reaction.

37. The method of claim 36, further comprising  
identifying at least one gene that encodes said protein  
that performs said at least one reaction.

25 38. The method of claim 35, further comprising  
identifying at least one compound that alters the activity or amount of said at least one participant,  
thereby identifying a candidate drug or agent that  
30 alters a *Homo sapiens* physiological function.

39. The method of claim 21, further comprising:

- (e) providing a modified constraint set, wherein said modified constraint set comprises a changed constraint for at least one reaction compared to the constraint for said at least one reaction in the data structure of part (a), and
- (f) determining at least one flux distribution

10 that minimizes or maximizes said objective function when said modified constraint set is applied to said data structure, thereby predicting a *Homo sapiens* physiological function.

40. The method of claim 39, further comprising

15 identifying at least one participant in said at least one reaction.

41. The method of claim 40, wherein said identifying at least one participant comprises

20 associating a *Homo sapiens* protein with said at least one reaction.

42. The method of claim 41, further comprising

identifying at least one gene that encodes said

25 protein.

43. The method of claim 40, further comprising

identifying at least one compound that alters the activity or amount of said at least one participant,

30 thereby identifying a candidate drug or agent that alters a *Homo sapiens* physiological function.

44. The method of claim 21, further comprising providing a gene database relating one or more reactions in said data structure with one or more genes 5 or proteins in *Homo sapiens*.

45. A method for predicting a *Homo sapiens* physiological function, comprising:

(a) providing a data structure relating a plurality of *Homo sapiens* reactants to a plurality of 10 *Homo sapiens* reactions,

wherein each of said *Homo sapiens* reactions comprises a reactant identified as a substrate of the reaction, a reactant identified as a product of the reaction and a stoichiometric coefficient relating said 15 substrate and said product,

wherein at least one of said *Homo sapiens* reactions is a regulated reaction;

(b) providing a constraint set for said plurality of *Homo sapiens* reactions, wherein said 20 constraint set includes a variable constraint for said regulated reaction;

(c) providing a condition-dependent value to said variable constraint;

(d) providing an objective function, and

25 (e) determining at least one flux distribution that minimizes or maximizes said objective function when said constraint set is applied to said data structure, thereby predicting a *Homo sapiens* physiological function.

30 46. The method of claim 45, wherein said value

provided to said variable constraint changes in response to the outcome of at least one reaction in said data structure.

47. The method of claim 45, wherein said  
5 value

provided to said variable constraint changes in response to the outcome of a regulatory event.

48. The method of claim 45, wherein said  
10 value

provided to said variable constraint changes in response to time.

49. The method of claim 45, wherein said  
15 value

provided to said variable constraint changes in response to the presence of a biochemical reaction network participant.

50. The method of claim 49, wherein said  
participant is selected from the group consisting of a  
substrate, product, reaction, enzyme, protein,  
20 macromolecule and gene.

51. The method of claim 45, wherein a plurality of said reactions are regulated reactions and said constraints for said regulated reactions comprise variable constraints.

25 52. A method for predicting *Homo sapiens* growth, comprising:

(a) providing a data structure relating a plurality of *Homo sapiens* skeletal muscle cell reactants to a plurality of *Homo sapiens* skeletal  
30 muscle cell reactions,

wherein each of said *Homo sapiens* reactions comprises a reactant identified as a substrate of the reaction, a reactant identified as a product of the reaction and a stoichiometric coefficient relating said substrate and said product;

(b) providing a constraint set for said plurality of *Homo sapiens* reactions;

(c) providing an objective function, and

(d) determining at least one flux

10 distribution that minimizes or maximizes said objective function when said constraint set is applied to said data structure, thereby predicting *Homo sapiens* skeletal muscle cell energy production.

53. A method for making a data structure relating a plurality of *Homo sapiens* reactants to a plurality of *Homo sapiens* reactions in a computer readable medium or media, comprising:

(a) identifying a plurality of *Homo sapiens* reactions and a plurality of *Homo sapiens* reactants 20 that are substrates and products of said *Homo sapiens* reactions;

(b) relating said plurality of *Homo sapiens* reactants to said plurality of *Homo sapiens* reactions in a data structure,

25 wherein each of said *Homo sapiens* reactions comprises a reactant identified as a substrate of the reaction, a reactant identified as a product of the reaction and a stoichiometric coefficient relating said substrate and said product;

(c) determining a constraint set for said plurality of *Homo sapiens* reactions;

(d) providing an objective function;

(e) determining at least one flux

30 distribution that minimizes or maximizes said objective

function when said constraint set is applied to said data structure, and

(f) if said at least one flux distribution is not predictive of a *Homo sapiens* physiological function, then adding a reaction to or deleting a reaction from said data structure and repeating step (e),

if said at least one flux distribution is predictive of a *Homo sapiens* physiological function, then storing said data structure in a computer readable medium or media.

54. The method of claim 53, wherein a reaction in said data structure is identified from an annotated genome.

55. The method of claim 54, further comprising storing said reaction that is identified from an annotated genome in a gene database.

56. The method of claim 53, further comprising annotating a reaction in said data structure.

57. The method of claim 56, wherein said annotation is selected from the group consisting of assignment of a gene, assignment of a protein, assignment of a subsystem, assignment of a confidence rating, reference to genome annotation information and reference to a publication.

58. The method of claim 53, wherein step (b)

further comprises identifying an unbalanced reaction in said data structure and adding a reaction to said data structure, thereby changing said unbalanced reaction to a balanced reaction.

5               59. The method of claim 53, wherein said adding a reaction comprises adding a reaction selected from the group consisting of an intra-system reaction, an exchange reaction, a reaction from a peripheral metabolic pathway, reaction from a central metabolic 10 pathway, a gene associated reaction and a non-gene associated reaction.

60. The method of claim 59, wherein said peripheral metabolic pathway is selected from the group consisting of amino acid biosynthesis, amino acid 15 degradation, purine biosynthesis, pyrimidine biosynthesis, lipid biosynthesis, fatty acid metabolism, cofactor biosynthesis and transport processes.

61. The method of claim 53, wherein said 20 *Homo sapiens* physiological function is selected from the group consisting of growth, energy production, redox equivalent production, biomass production, production of biomass precursors, production of a protein, production of an amino acid, production of a 25 purine, production of a pyrimidine, production of a lipid, production of a fatty acid, production of a cofactor, transport of a metabolite, development, intercellular signaling, and consumption of carbon nitrogen, sulfur, phosphate, hydrogen or oxygen.

30               62. The method of claim 53, wherein said *Homo sapiens* physiological function is selected from the group consisting of degradation of a protein,

degradation of an amino acid, degradation of a purine, degradation of a pyrimidine, degradation of a lipid, degradation of a fatty acid and degradation of a cofactor.

5 63. The method of claim 53, wherein said  
data

structure comprises a set of linear algebraic  
equations.

10 64. The method of claim 53, wherein said  
data  
structure comprises a matrix.

15 65. The method of claim 53, wherein said  
flux  
distribution is determined by linear programming.

66. A data structure relating a plurality of *Homo sapiens* reactants to a plurality of *Homo sapiens* reactions, wherein said data structure is produced by a process comprising:

20 (a) identifying a plurality of *Homo sapiens* reactions and a plurality of *Homo sapiens* reactants that are substrates and products of said *Homo sapiens* reactions;

25 (b) relating said plurality of *Homo sapiens* reactants to said plurality of *Homo sapiens* reactions in a data structure,

30 wherein each of said *Homo sapiens* reactions comprises a reactant identified as a substrate of the reaction, a reactant identified as a product of the reaction and a stoichiometric coefficient relating said substrate and said product;

- (c) determining a constraint set for said plurality of *Homo sapiens* reactions;
- (d) providing an objective function;
- (e) determining at least one flux distribution that minimizes or maximizes said objective function when said constraint set is applied to said data structure, and
- (f) if said at least one flux distribution is not predictive of *Homo sapiens* physiology, then adding a reaction to or deleting a reaction from said data structure and repeating step (e),
  - if said at least one flux distribution is predictive of *Homo sapiens* physiology, then storing said data structure in a computer readable medium or media.

1/4

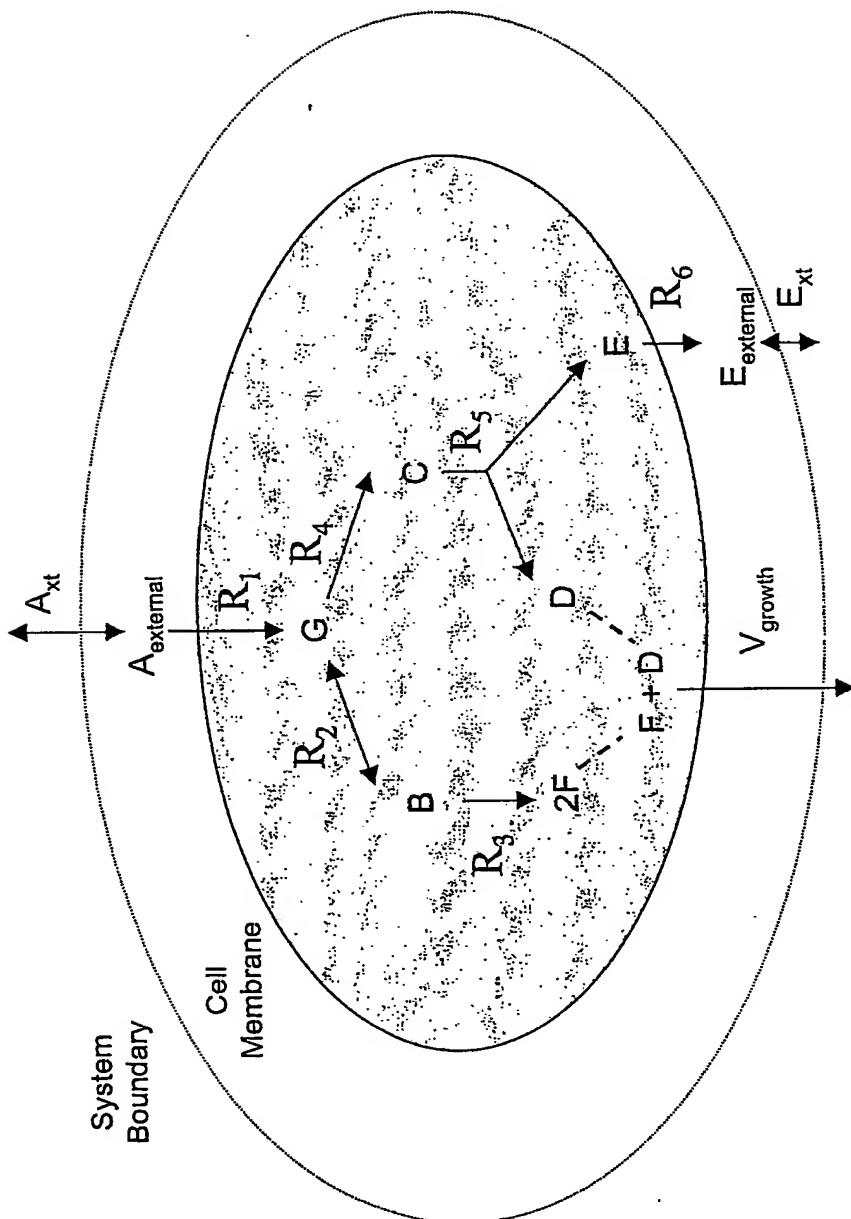


FIGURE 1

BEST AVAILABLE COPY

Mass Balances	Flux Constraints
$G : R_1 - R_2 - R_4 = 0$ $B : R_2 - R_3 = 0$ $C : R_4 - R_5 = 0$ $D : R_5 - V_{\text{growth}} = 0$ $E : R_5 - R_6 = 0$ $F : 2R_3 - V_{\text{growth}} = 0$ $A_{\text{external}} : -A_{\text{xt}} - R_1 = 0$ $E_{\text{external}} : R_6 - E_{\text{xt}} = 0$	$0 \leq R_1 \leq \infty$ $-\infty \leq R_2 \leq \infty$ $0 \leq R_3 \leq \infty$ $0 \leq R_4 \leq \infty$ $0 \leq R_5 \leq \infty$ $0 \leq R_6 \leq \infty$ $0 \leq V_{\text{growth}} \leq \infty$ $Y_1 \leq A_{\text{xt}} \leq Y_1$ $-\infty \leq E_{\text{xt}} \leq 0$
<b>Objective Function</b> $Z = V_{\text{growth}}$	

FIGURE 2

$$\begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} = \begin{bmatrix} R_1 \\ R_2 \\ R_3 \\ R_4 \\ R_5 \\ R_6 \\ V^{\text{growth}} \\ A_{xt} \\ E_{xt} \end{bmatrix}$$

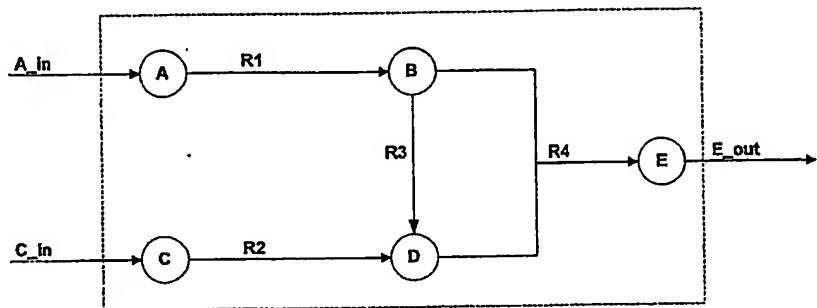
$$\begin{array}{ll}
 R_6 & R_6 \quad V^{\text{growth}} \quad A_{xt} \quad E_{xt} \\
 R_5 & 0 \quad 0 \quad 0 \quad 0 \\
 R_4 & 0 \quad 1 \quad 0 \quad 0 \\
 R_3 & -1 \quad 0 \quad 1 \quad 0 \\
 R_2 & 1 \quad 0 \quad 0 \quad 0 \\
 R_1 & 0 \quad 0 \quad 0 \quad 0
 \end{array}$$

$$\begin{array}{ll}
 B & A_{\text{external}} \\
 C & \\
 D & \\
 E & \\
 F & \\
 G & \\
 \hline
 & E_{\text{external}}
 \end{array}$$

FIGURE 3

A)

## Example Biochemical Reaction Network



B)

## Example Regulatory Structure and Requirements

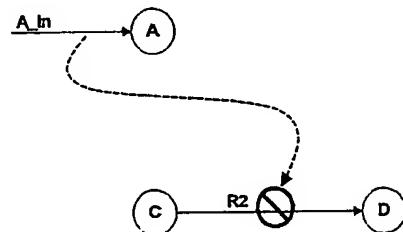


FIGURE 4

**This Page is Inserted by IFW Indexing and Scanning  
Operations and is not part of the Official Record**

## **BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- BLACK BORDERS**
- IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- FADED TEXT OR DRAWING**
- BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- SKEWED/SLANTED IMAGES**
- COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- GRAY SCALE DOCUMENTS**
- LINES OR MARKS ON ORIGINAL DOCUMENT**
- REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- OTHER:** \_\_\_\_\_

---

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.**

THIS IS THE U.S. PATENT AND TRADEMARK OFFICE (USPTO)